BOSTON PUBLIC LIBRARY
3 9999 06316 449 3

RJ 399
P5 U5
1964

№ *RJ399.P5U5 1964

THE TRUSTEES OF THE PUBLIC LIBRARY OF THE CITY OF BOSTON
1852 · 1878

GIVEN BY

U. S. SUPT. OF DOCUMENTS

THE CLINICAL TEAM LOOKS AT PHENYLKETONURIA

Boston Public Library
Superintendent of Documents

AUG 31 1964

DEPOSITORY

U. S. DEPARTMENT
of HEALTH,
EDUCATION,
and WELFARE

Welfare Administration

Children's Bureau

1961
revised 1964

Treating the disease but forgetting the child is a familiar phrase which has been applied to many diseases. The problem of phenylketonuria aptly falls into this category. The initial approach for treating this disease purely from a medical and nutritional point of view is not longer tenable in light of experience during the last few years.

The contributions of several disciplines are all important in the proper management of this disease. It is true that the medical aspects are extremely important, but it is hoped that the following papers by a multidisciplinary team working with these children will alert others to the many problems encountered in providing proper guidance to these families.

The Children's Bureau is pleased to reproduce and make these papers available.

U.S. Children's Bureau
"

THE CLINICAL TEAM LOOKS AT PHENYLKETONURIA

Problems of the disease from the viewpoint of the biochemist, pediatrician, medical social worker, public health nurse, psychologist and nutritionist.

First Printed 1961
Revised 1964

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Welfare Administration
Children's Bureau
1964

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C., 20402 - Price 40 cents

*RJ 399
.P5U5
1964

THE CLINICAL TEAM LOOKS AT PHENYLKETONURIA

BIOCHEMICAL ASPECTS OF PHENYLKETONURIA

Kenneth N. F. Shaw, Ph.D., Senior Research Fellow, Division of Chemistry, California Institute of Technology, and Director of Laboratories, Clinical Research Center, Childrens Hospital, Los Angeles, California.

PEDIATRIC ASPECTS OF PHENYLKETONURIA

Richard Koch, M.D., Assistant Professor of Pediatrics, Department of Pediatrics of the University of Southern California, and Director, Child Development Clinic, Childrens Hospital of Los Angeles, California.

FAMILY ATTITUDES AND THE LOW PHENYLALANINE DIET

Sylvia Schild, M.S.W., Casework Specialist, Child Development Clinic, Childrens Hospital, Instructor in Social Work, Department of Pediatrics, U.S.C. School of Medicine, Los Angeles, California.

PHENYLKETONURIA: NURSING RESPONSIBILITY

Nancy Ragsdale, R.N., M.P.H., Public Health Nursing Consultant, Child Development Clinic, Childrens Hospital of Los Angeles, California.

PSYCHOLOGICAL ASPECTS OF PHENYLKETONURIA

Karol Fishler, Ph.D., Chief Clinical Psychologist, Child Development Clinic, Childrens Hospital of Los Angeles, California,

NUTRITIONAL ASPECTS OF PHENYLKETONURIA

Phyllis B. Acosta, M.D., Assistant Director, School of Dietetics, Loma Linda University, Los Angeles, California.

BIOCHEMICAL ASPECTS OF PHENYLKETONURIA

By

Kenneth N. F. Shaw, Ph.D.

Phenylketonuria was described originally by Asbjörn Fölling in Norway in 1934. This was the first disease shown to involve a specific genetically controlled biochemical defect, a feature of historical importance in the development of a rational understanding of mental retardation.

Some of the important characteristics of phenylketonuria may be summarized briefly. Mental retardation usually is severe, with 90% of the untreated patients having an intelligence quotient less than 50. Neurological disturbances parallel the degree of mental defect and may include convulsive seizures, hyper-activity, poor attention span, and an abnormal electroencephalogram. Pigmentation in the phenylketonuric usually is less than in other normal members of his family, and many older patients have blue eyes, blond hair and a fair skin, not infrequently with eczema or other skin disorders. Attainment of developmental landmarks is delayed, but overall physical development is not abnormal. In the past, life expectancy has been somewhat less than normal, partly because of susceptibility to infection and because of the prevalence of certain infectious diseases among institutionalized patients.

Phenylketonuria is found in either sex and is transmitted by an autosomal recessive gene. This means that the patient is a homozygote with a pair of defective genes, whereas each parent is a heterozygote with one defective gene: i.e., a carrier. Heterozygote carriers are clinically normal and do not have any of the gross manifestations of phenylketonuria. The genetic status of children born from marriages of two heterozygote parents shows a Mendelian distribution: 1 entirely normal, 2 heterozygote carriers (clinically normal), 1 phenylketonuric. It should be emphasized, however, that this 1:2:1 ratio is statistical and that in these families each birth involves a 1-in-4 chance that the child will have phenylketonuria.

Phenylketonuria has been encountered mostly in peoples of northern and western European origin, but also has been recognized in Yemenite Jews, Japanese and other races. Estimates of incidence have ranged from 1-in-10,000 to 1-in-40,000 for patients, and 1-in-50 to 1-in-100 for carriers, and vary according to the age distribution and locale of the population surveyed. Approximately 1% of institutionalized mentally defective patients are phenylketonurics.

The primary biochemical consequence of the defective gene in phenylketonuria is an inability to convert phenylalanine to tyrosine. Phenylalanine, which is an amino acid essential for growth and maintenance, is present in all ordinary foods where it constitutes 4-to-6% of proteins from which it is released by digestion. In the normal individual, some is utilized for synthesis of tissue proteins, and the remainder is oxidized by an enzyme in the liver to the amino acid tyrosine. Tyrosine also is built into various proteins, a small amount is used for synthesis of norepinephrine, epinephrine, the thyroid hormones, and melanin pigments, and the rest is oxidized in a series of steps to carbon dioxide and water. These features are summarized in Figure 1. In phenylketonuria, the liver enzyme phenylalanine hydroxylase is inactive. Because of this metabolic block, phenylalanine accumulates in the blood (20-40 times normal) and cerebrospinal fluid, and it spills over into the urine (30-50 times normal).

In phenylketonuria, the metabolism of phenylalanine is diverted into various paths which have little importance in the normal individual, as illustrated in Figure 2. The urine levels of several metabolites which normally are small increase immensely. One of them, phenylpyruvic acid, is a phenyl ketone after which the disorder is named; more than 1 gm. per day may be excreted by the phenylketonuric compared to negligible amounts by normal subjects. Another metabolite, phenylacetic acid, is responsible for the mousy smell typical of many phenylketonuric patients. The related substances phenylacetylglutamine and phenyllactic acid also are excreted in quantity, but are not detected readily. The phenolic metabolite o-hydroxyphenylacetic acid can be visualized easily on paper chromatograms: several hundred mg. per day are excreted by a phenylketonuric, but only about 1 mg. per day by a normal individual.

The biochemical abnormalities found in phenylketonuria provide the basis for analytical procedures which facilitate detection, diagnosis and management of patients.

1. Phenylpyruvic acid

This acid is detected readily in phenylketonuric urine by the vivid green color formed when ferric chloride solution is added. The commercial "Phenistix," which contains a buffered ferric reagent, also makes use of this reaction. This test has been applied to urine on diapers, and also to urine dried on filter paper. Phenylpyruvic acid is unstable, however, and optimal results are obtained only with a fresh urine specimen or one which has been frozen promptly after collection.

A second effective test for phenylpyruvic acid in urine depends upon reaction with dinitrophenylhydrazine reagent to give a turbid yellow precipitate.

2. Phenylalanine

   a. Guthrie inhibition assay: a microbiological procedure particularly suited for rapid screening of large numbers of patients.

   b. Paper chromatography: inexpensive, specific, fairly rapid, and semiquantitative.

FIGURE 1

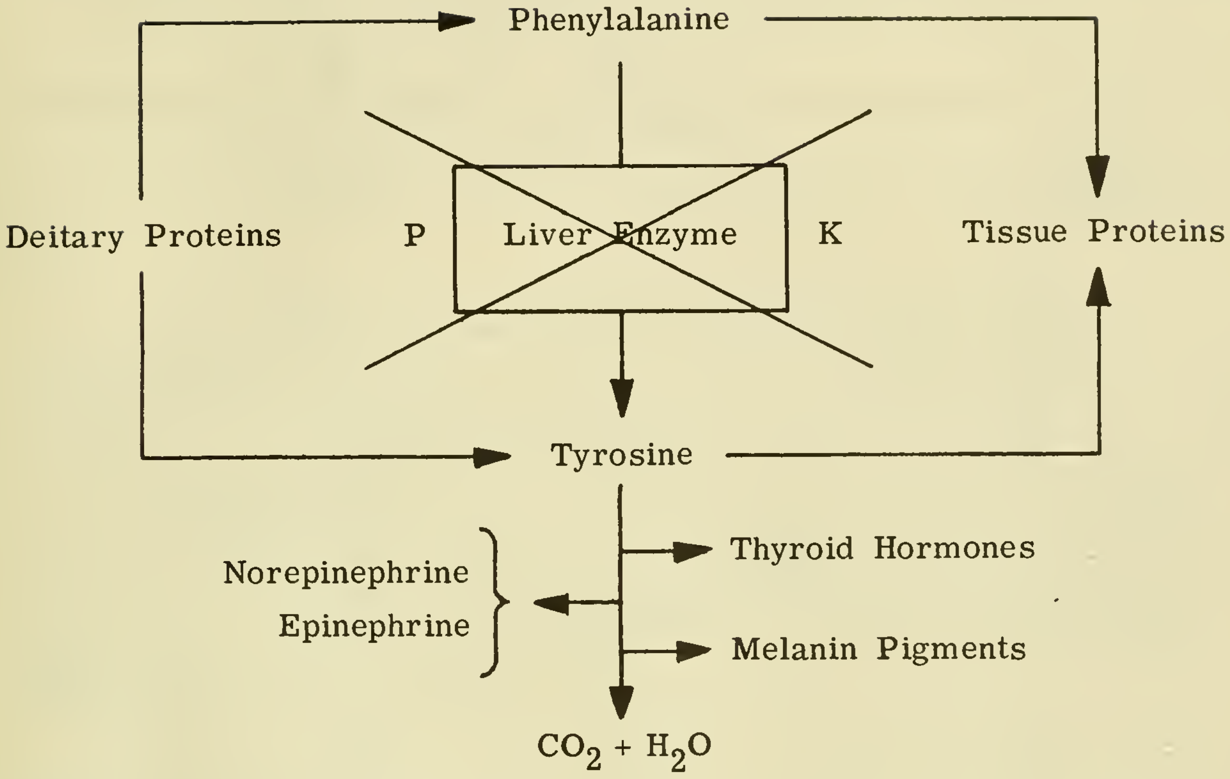
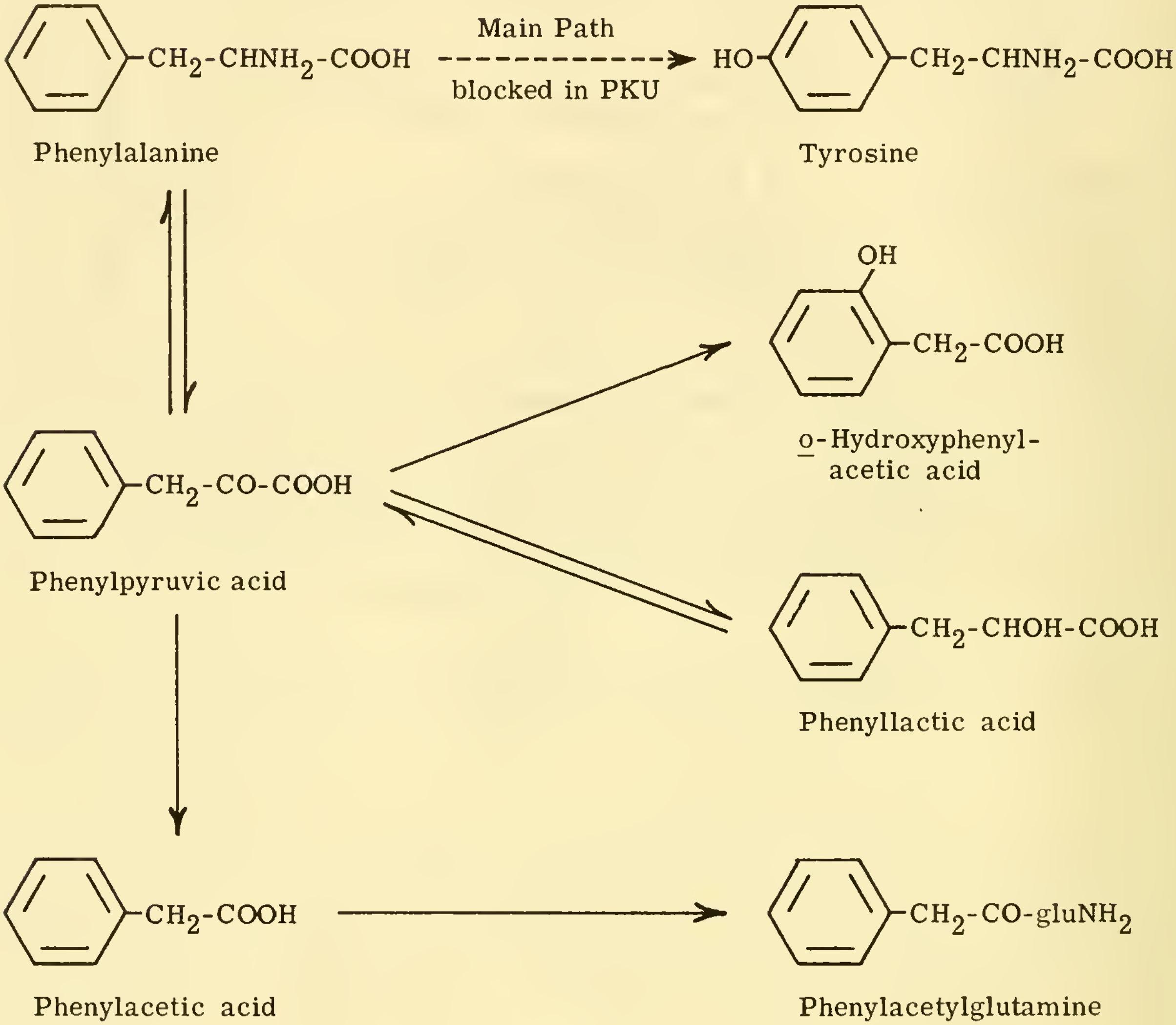

Phenylalanine
Deitary Proteins
P
Liver Enzyme
K
Tissue Proteins
Tyrosine
Norepinephrine
Epinephrine
Thyroid Hormones
Melanin Pigments
$CO_2 + H_2O$

FIGURE 2: METABOLIC PATHS OF PHENYLALANINE IN PHENYLKETONURIA



c. Chemical and enzymatic methods: not suitable for large-scale screening but important for proper management of the patient after diagnosis. Several different procedures are available which provide precise results if analytical conditions are well controlled.

3. o-Hydroxyphenylacetic acid

Easy visulization of this compound on 1-dimensional paper chromatograms prepared from phenylketonuric urine provides a simple confirmatory diagnostic test.

Excessive quantities of phenylalanine metabolites are present not only in urine and blood of phenylketonuric patients but also in tissues where they interfere with metabolism of the amino acids tyrosine and tryptophan. This phenomenon has been invoked to explain lower than normal blood levels of norepinephrine and epinephrine, which are derived from tyrosine, and serotonin, which is formed from tryptophan. These hormones are important in functioning of the central nervous system. Interference with the production of melanin pigments from tyrosine likewise accounts for the diminished pigmentation of phenylketonurics. The secondary disturbance of tyrosine and tryptophan metabolism also is reflected in the appearance of appreciable amounts of unusual metabolites of these amino acids in urine, namely, o-hydroxphenylacetic and indoletactic acids. Very little of these compounds is found in normal urines.

Several hypotheses have been offered to explain the relation of the biochemical abnormalities to the mental defect in phenylketonuria. A simple explanation in terms of a specific toxic effect is not tenable, inasmuch as none of the abnormal metabolites show a significant direct action on the central nervous system. Inhibitory action by phenylalanine or some of its metabolites upon certain essential enzyme systems has been demonstrated in experiments carried out in vitro. The significance of studies should not be overestimated, however, since compounds frequently have been tested at levels much higher than those encountered in vitro, even in the phenylketonuric patient. It may be mentioned that the mental state is not improved by measures which raise the low levels of norepinephrine, epinephrine or serotonin, and therefore a direct involvement of these hormones seems unlikely. It is also noteworthy that the degree of mental retardation shows no correlation with the abnormal levels of metabolites or hormones. Recent work has shown that a high level of phenylalanine interferes with the transport of other important amino acids across the blood-brain barrier. The possibility of a similar interference with intestinal absorption of amino acids is apparent from the observation that the levels of several amino acids in serum of phenylketonuric patients are appreciably lower than normal. Thus, it is conceivable that some degree of cellular dysfunction in the brain and other tissues of the phenylketonuric may arise from localized amino acid imbalance resulting from impaired transport.

Another line of investigation has been concerned with the possibility that structural alteration in the phenylketonuric brain may be responsible for defective function. In this regard, no well-defined pathological changes have been noted, but tendencies toward a smaller brain and a delay in myelinization have been observed. Of possible pertinence are reports that white matter has a lower than normal content of cerebrosides and cholesterol, and that certain phenylalanine metabolites have an adverse effect upon cholesterol synthesis.

From the foregoing it may be seen that data on pathogenesis of the mental defect in phenylketonuria are still incomplete, and that further research is required to permit integration of the several lines of thought. Understanding of the various hypotheses may be facilitated by considering the way in which the disorder develops. The phenylketonuric patient is clinically normal at birth. The various metabolites appear at different times in the first few weeks of life and provide an increasingly abnormal biochemical environment in a period during which the brain still is undergoing active differentiation and development. The result is progressive irreversible damage.

A primary causative role for phenylalanine in phenylketonuria is evident, even though the detailed mechanism of mental defect and brain damage is incompletely defined. When the amount of phenylalanine in the diet is regulated carefully, the blood level of this amino acid decreases to a normal value and other biochemical abnormalities disappear rapidly. Many of the neurological signs also are eliminated. It should be emphasized that a small amount of phenylalanine still must be provided in the diet for synthesis of tissue proteins, particularly in the growing child. This approach constitutes the only effective treatment for phenylketonuria. The extent to which mental defect can be prevented or minimized depends upon how soon in life the special low phenylalanine diet is started and how well it is maintained. Dietary treatment usually does not seem to result in major improvement in mental status after the patient is 3 years old, but still may be worthwhile for various reasons. These features underline the urgent need for early diagnosis and continuous control.

The successful application of the biochemical approach to phenylketonuria makes it appropriate to recall a statement Asbjörn Fölling made 25 years ago: "The study of phenylpyruvic amentia may throw light on the whole problem of mental deficiency." In an area once clouded by social stigma, the hope expressed by Fölling now has become a challenge for investigators in the various basic and clinical sciences in a concerted attack on many mental diseases.

Summary

Phenylketonuria is an inherited disorder characterized by gross mental defect consequent to an inability to metabolize the amnio

acid phenylalanine in a normal manner. The only effective treatment involves restriction of the dietary intake of phenylalanine in order to restore normal levels in body fluids. Optimal results depend upon early diagnosis and careful dietary management.

REFERENCES*

1. Layman, Frank L. and other: PHENYLKETONURIA. Charles C Thomas, Springfield, Ill., 1963. 315 pp.

2. Knox, W. E., Stanbury, J. B., Wyngaarden, J. B., and Frederickson, D. S.: Phenylketonuria. In THE METABOLIC BASIS OF INHERITED DISEASE. McGraw-Hill Book Co., Inc., New York: 1960. Complete pgs. (p. 321-382).

* Several hundred papers have been published on phenylketonuria during the past 30 years. The many facets of knowledge concerning this disorder have been examined in detail and integrated efficiently in the two recent comprehensive reviews mentioned above.

PEDIATRIC ASPECTS OF PHENYLKETONURIA

By

Richard Koch, M.D.

Although phenylketonuria (PKU) has been known as a medical entity for over 20 years[1], treatment aimed at preventing the neurologic sequelae of the disease is quite recent[2-9]. The fact that the low phenylalanine diet minimizes or actually prevents brain damage is now well established [10-14]. The problem now is to establish screening programs so that children with this disease can be detected early enough for therapy to be instituted before brain damage occurs. The optimal age of diagnosis is during the neonatal period. Early diagnosis can be established in families where a previous child has been diagnosed with the disease, but is not so easily accomplished when the presence of the gene has not already been identified[15-17]. The recent development of a test for serum phenylalanine content utilizing a bacterial inhibition assay technique by Guthrie[18] may eliminate this difficulty. If so, it will be a valuable screening procedure suitable for use in the newborn nursery and obviate the need for the large scale screening programs for PKU which are now being conducted in many areas[19-21].

Observations

Thirty-one phenylketonuric patients observed in 23 families form the basic for this report. Ages at the time of diagnosis ranged from 5 days to 8 years. Nine patients were diagnosed prior to 1 year of age with the average age of diagnosis being 2 years and 4 months. Eighteen were male. Ethnic backgrounds revealed a predominance of Irish, English, Scotch, and German. None in our sample were Jewish or Negro. In 21 cases the diagnosis was suspected because of mental retardation; a total of five siblings were subsequently diagnosed because of identification of the index case. Recently two additional newborn siblings have been identified due to similar reasons. Only three children have been identified in routine screening programs: one at 4 weeks of age by diaper ferric chloride test in a pediatrician's office; one by similar testing at 4 months of age in a well baby clinic; and one by ferric chloride testing in a class for retarded children.

Irritability, hyperactivity, and mental retardation were characteristic of the older children. There was a tendency to obesity in younger children. Eczema occured in eight patients. Hair color varied. Sixteen had brown hair, nine were blond, five had red hair, and one was brunette. Only two patients exhibited seizures. In all cases the diagnosis was established by finding elevated serum phenylalanine content which ranged from 13-to-64 milligrams percent.* Electroencephalographic abnormality was noted in seven.

Results of Dietary Therapy

Only 24 of the 31 patients have been adequately treated with a low phenylalanine diet longer than 1 year. Four are not now being treated (cases 21, 25, 30, and 31) and four have been on therapy less than one year (cases 3, 5, 18, and 28). In spite of the relatively late age of initial diagnosis (average age 2 years, 4 months) nearly every child has shown improvement in behavior and developmental progress (Table I). Figure I shows the relationship of age of diagnosis to the developmental quotient. Note the gradual decline of DQ as the age of diagnosis increases, except for two cases (20 and 25). Infants diagnosed during the first 6 months of life all had DQ's over 75 compared to an average DQ of 35 in the children diagnosed after 2 years of age. Figure 2 reveals the changes in DQ/IQ ranging from 4 to 43 points for an average increase of 17 points in the treated patients. Note that even the children diagnosed over the age of 3 years show intellectual improvement with dietary therapy. Cases 1 and 2 were diagnosed at birth and have done well. The most spectacular gains occured in Case 8 who was diagnosed at 8 months with a developmental quotient of 37. At 5 years of age his IQ was 79. (Figure 3) Another youngster (case 26), age 3 years and 2 months, was put on dietary therapy at the insistence of the mother. His initial IQ was 10. Much to our amazement he has made steady progress and his most recent IQ, at 7 years of age, was 53. At present he is in a class for educable mentally retarded children, has developed language ability and behaves nicely. Another 5 year old boy (case 29) was put on dietary therapy because of severe uncontrollable behavior. IQ at the time therapy was instituted was 26. He calmed down remarkably and at present is attending a school for retarded children and has developed speech patterns. His most recent IQ was 37, using the Stanford-Binet test. Case 24 posed a particularly difficult problem in management. The child is one of five children of somewhat incompetent parents. Satisfactory dietary control was never achieved. In spite of this some progress was made and at age 5-1/2 her IQ was 40. She was institionalized and dietary therapy discontinued. She regressed so rapidly that the parents became alarmed, removed her from the institution, and have once more resumed dietary therapy.

Four of our cases are not being treated. One patient (case 25) has superior intelligence and dietary therapy has not been advised. In the other three, the children were already severely defective at the time the diagnosis was established. The mothers were unable to manage the diet because of the older age of the children. Two are already institutionalized.

* The flourimetric method of McCowan and Robbins was utilized for this study.

TABLE I

DQ CHANGES IN 31 PKU CHILDREN

WITH OR WITHOUT TREATMENT

Case No.	Age Diagnosed	Initial DQ/IQ	Dietary Control*	Latest DQ/IQ	DQ/IQ Change	Diet Duration	Present Age
1	Birth	104	Excellent	100	-4	1-1	1-1
2	Birth	100	Excellent	94	-6	1-9	1-9
3	0-1	108	Excellent	108	-	0-8	0-8
4	0-6	75	Good	83	+8	1-0	1-6
5	0-7	57	-	-	-	0-4	0-11
6	0-7	81	Excellent	74	-7	1-2	1-9
7	0-7	37	Excellent	73	+36	1-4	1-11
8	0-8	37	Excellent	75	+38	4-3	4-11
9	0-10	84	Excellent	101	+17	1-5	2-3
10	0-12	61	Good	77	+16	1-8	2-8
11	1-1	31	Good	52	+21	2-7	3-8
12	1-2	62	Good	73	+11	3-10	5-0
13	1-2	40	Excellent	68	+28	6-2	7-4
14	1-2	30	Poor	29	-1	3-6	4-8
15	1-6	49	Good	86	+37	1-5	2-11
16	1-6	46	Good	62	+16	1-9	3-3
17	1-7	66	Excellent	72	+6	1-0	2-7
18	1-9	45	-	-	-	0-1	1-10
19	1-10	48	Good	59	+11	1-10	3-8

CONTINUED

TABLE I Cont'd.

Case No.	Age Diagnosed	Initial DQ/IQ	Dietary Control*	Latest DQ/IQ	DQ/IQ Change	Diet Duration	Present Age
20	1-10	98	Excellent	102	+4	2-3	4-1
21	2-0	NM**	Poor (discont'd)	NM**	-	1-6	10-0
22	2-1	50	Excellent	67	+16	2-8	4-9
23	2-6	43	Good	76	+33	3-11	6-5
24	2-6	30	Poor	40	+10	3-4	5-10
25	3-0	132	None	124	-8	-	7-0
26	3-2	10	Good	53	+43	3-9	7-9
27	4-6	29	Poor	28	-1	2-1	6-7
28	4-8	46	-	-	-	0-1	4-9
29	5-5	26	Good	37	+11	2-7	8-0
30	8-0	NM**	None	NM**	-	-	15-10
31	8-4	27	Poor (discont'd)	10	-17	1-0	10-4

* Excellent control indicates serum phenylalanine content less than 6 mg.%.
Good control indicates 6-12 mg.%.
Poor control, serum levels above 12 mg.%.

** NM - Abbreviation for not measurable.

FIGURE 3: DQ/IQ DISTRIBUTION AT THE TIME OF PKU DIAGNOSIS

N=31

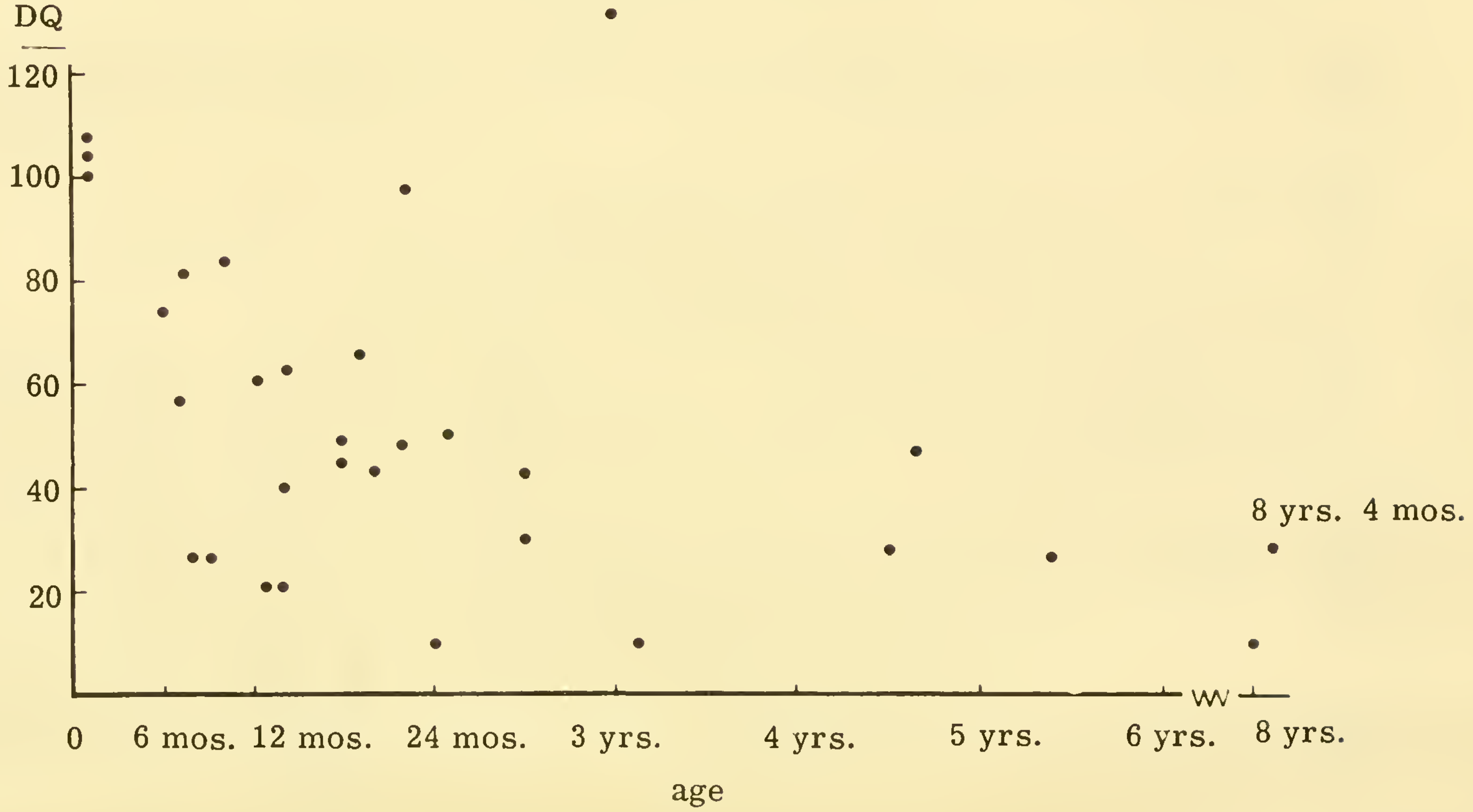


FIGURE 4: COMPARISON OF MEAN INITIAL DQ's AT THE TIME OF PKU DIAGNOSIS WITH MEAN LATEST DQ's OR IQ's

N=23

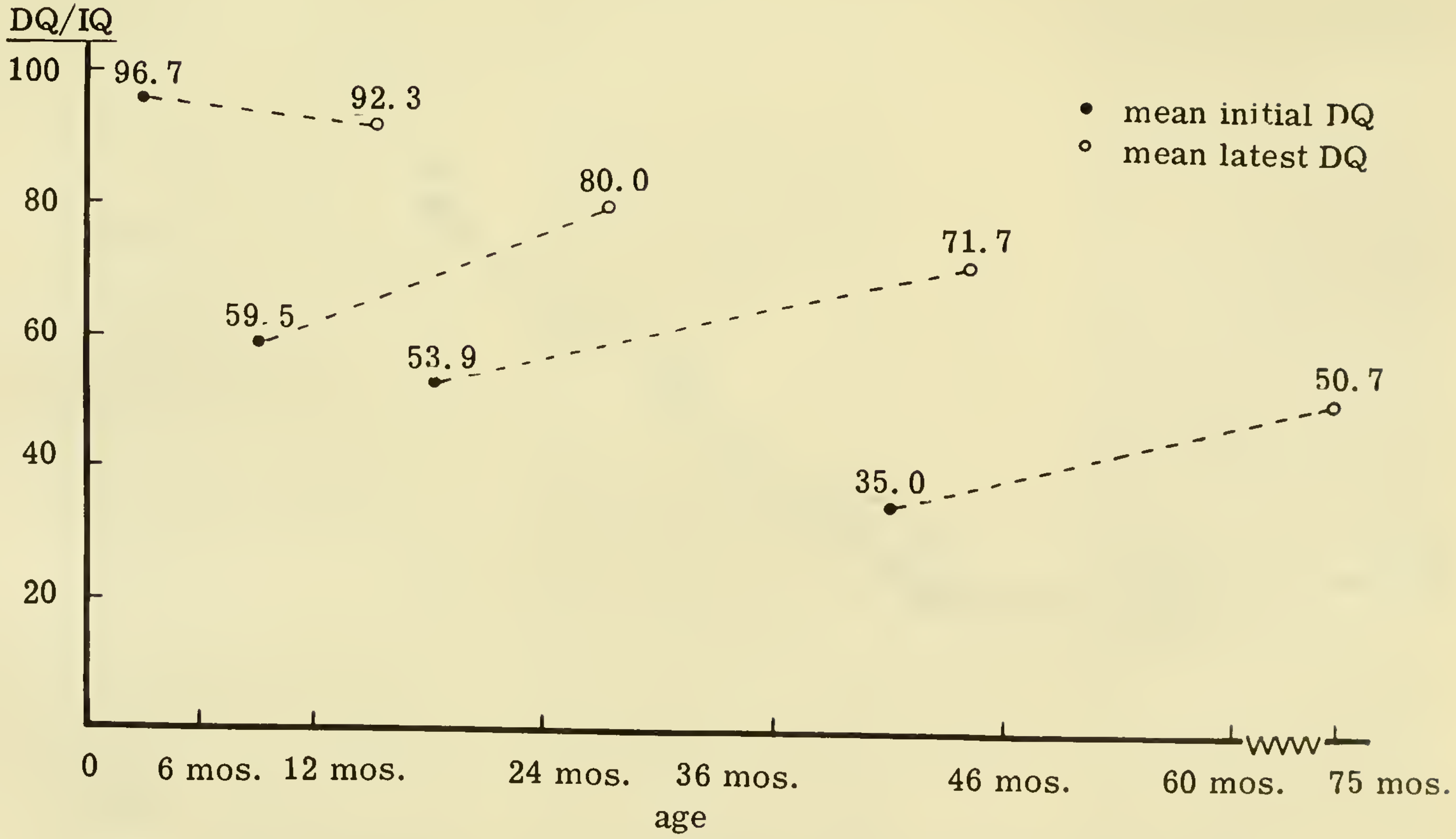
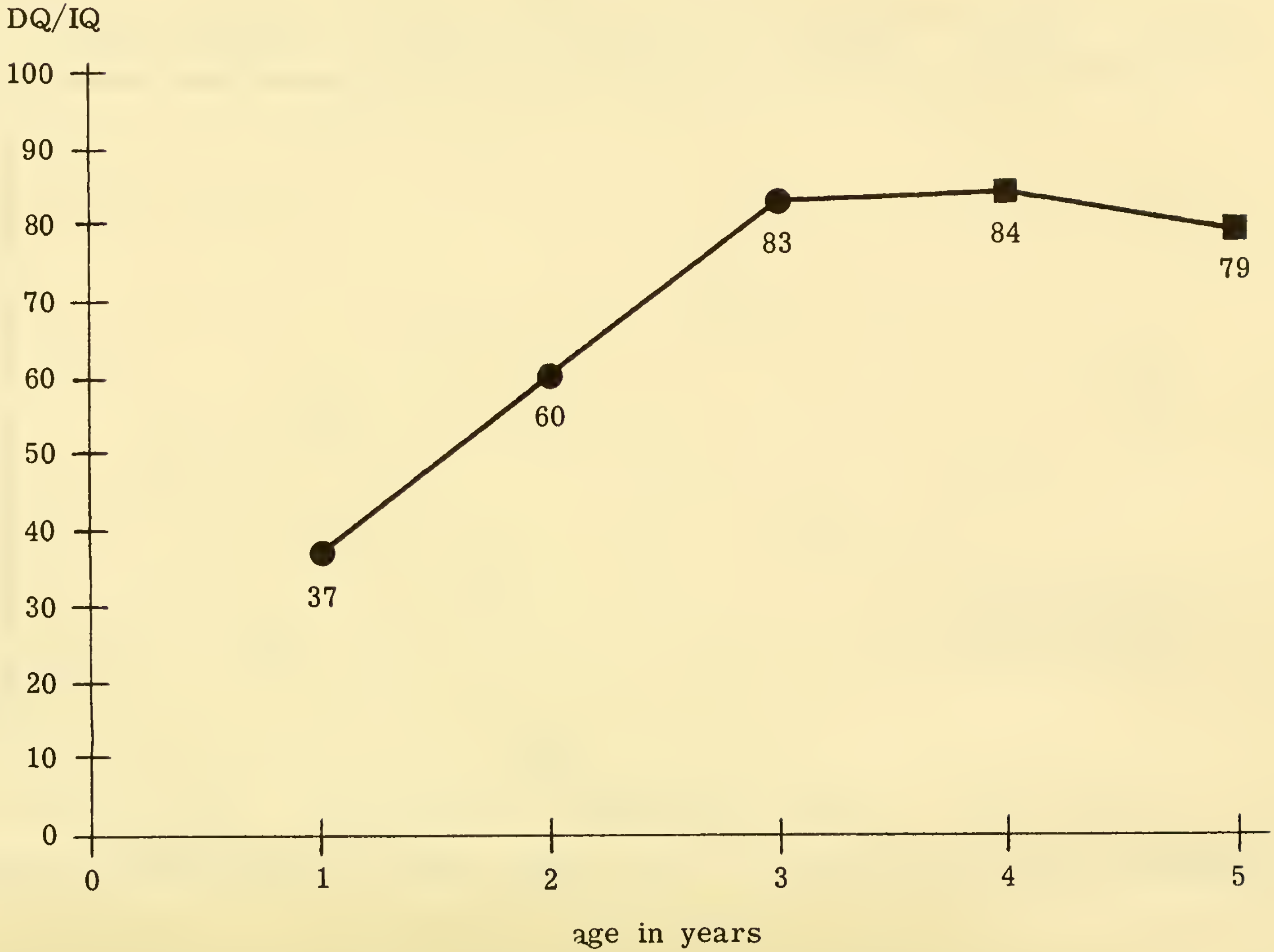


FIGURE 5: DQ/IQ DATA IN CHILD WITH PHENYLKETONURIA (PKU)



Recently we saw a 7 year old phenylketonuric patient who was treated elsewhere from 16 months to 4 years of age by the low phenylalanine diet. Her intelligence quotient at the time of diagnosis was not determined, however a value of 89 is recorded for age 4 when dietary therapy was discontinued. The score was obtained by the Stanford-Binet test. She seemed to do fairly well for two years although she was more restless, irritable, and sleepless than she had been on the diet. At age 6-1/2 years she began to experience psychomotor seizures. Electroencephalogram revealed diffuse abnormality with spike foci. Serum phenylalaine at the time she was seen was elevated to 34 milligrams percent. Her growth pattern was normal and no eczema was noted although she was slightly blonder than when the diet was discontinued. Intelligence testing revealed an IQ of 88 on the Stanford-Binet Scale.

Discussion

Most of the large surveys of PKU children in the literature are based upon institutionalized populations[8,22,23,24]. The most frequent signs and symptoms mentioned in previous reports are mental deficiency, blond hair, blue eyes, and seizures. Only recently has there been emphasis on vomiting, eczema and urine odor as early signs in infancy[25]. Eight of our patients had been taken to physicians frequently because of persistent eczema unresponsive to usual therapy without the diagnosis of PKU being established. In each the onset of eczema preceded the development of mental retardation. Obesity, in our experience, is characteristic of the infant with PKU and sometimes leads to a mistaken diagnosis of hypothyroidism because of the accompanying mental retardation. In fact, three were treated with thyroid because their physicians strongly suspected hypothyroidism in spite of normal blood protein-bound iodine values.

The PKU child is usually hyperactive and exhibits unpredictable erratic behavior. Excessive rocking movements, grinding of teeth, arm waving, and overall aimless behavior occasionally are misdiagnosed as early childhood schizophrenia. Five of our cases were considered autistic until the identifying urine test for phenylpyruvic acid revealed the true basis for their behavior. While blond hair, blue eyes, seizures and mental deficiency may be characteristic of older children with this disease, these signs are not regularly found in younger infants. For example, only two of our patients exhibited minor seizures; one myoclonic and one petit mal. The marked contrast in the signs and symptoms manifested by our patients is undoubtedly due to their young age. Thus only by routine screening of patients can even the experienced clinician avoid making errors in diagnosis[26]. This points up the value of routine testing in various clinics, such as child guidance, epilepsy, eczema, etc.

It has been our practice to put all newborn siblings of known PKU patients on a low phenylalanine diet on the fifth day of life. Simultaneously a serum phenylalanine level is obtained. The infant then is maintained on dietary therapy until the serum phenylalaine content is known. If the serum level is below 5 milligrams per cent, a normal diet can be safely resumed. Urine tests for phenylpyruvic acid then can be relied upon for further confirmation for absence of the disease. On the other hand, if the serum value for phenylalanine is greater than 5 milligrams per cent, the diet is maintained, and the infant considered phenylketonuric. Further confirmation of the diagnosis should be obtained at one to two years of age. Reasons for such early conservative therapy are the following:

1) Renal immaturity during early infancy results in higher initial serum phenylalanine content[27], perhaps resulting in greater cerebral damage.

2) The rapid growth of the brain during early infancy suggests it may be more susceptible to damage at this time.

3) The lag in being able to obtain prompt serum phenylalanine determination due to the fact that few laboratories perform this test routinely.

The decision as to whether an older child should be treated with the low phenylalanine diet is difficult. General agreement exists among physicians that all PKU patients less than 3 years of age should be treated. Centerwall points out, however, that selected older children deserve a clinical trial of dietary therapy and that results in older children are only apparent after months to years of careful treatment[28]. Our experience would substantiate his observations. For example: two of our patients have made good progress in spite of apparent severe mental defect present at the time therapy was begun. Whether to treat PKU children with normal intelligence with dietary therapy is another difficult problem. One of the PKU cases that we are now following was previously reported by Harold Caudle[29]. At that time the patient was 2 years and 9 months old, with an IQ of 134. At present he is 7 years old and has an IQ of 128. Phenylalanine serum values have ranged from 10 milligrams per cent to 17 milligrams per cent. His electroencephalogram and skeletal bone age are normal. His only dietary restriction is due to the fact his mother does not allow him milk. Whether he should be treated with dietary therapy is a matter of concern[30,31].

Horner[32] has reported on three patients in whom dietary therapy was discontinued at age 4 years. His report suggested that the children seemed to be doing well following discontinuance of dietary therapy although the observation period was admittedly short in one patient. Our observations in the child who was institutionalized and in the child with the onset of seizures suggest that discontinuance of dietary therapy may be more hazardous than previously thought. The observations of Bickel would tend to support this latter conslusion. In fact Bickel[31] suggests that therapy should be continued at least until adolescence.

When treatment has been initiated, every effort is made to maintain the serum phenylalanine content below 6 milligrams per cent. To maintain the level below three milligrams per cent as recommended by Bickel[14] and Kretchmer[33] has been difficult with older children in our experience. When too many restrictions on their diet are demanded, the older children generally do not cooperate readily and obtain forbidden foods from neighbors, schoolmates and the family refrigerator.

Phenylketonuria is a disease requiring the skills of several disciplines[34,35]. Parents have many questions and problems which can be adequately handled by others. The disciplines of nutrition, social work, public health nursing and psychology are indispensable for a well rounded program. The nutritionist[36] can be very helpful in making the diet more acceptable, especially to the older child. She can also help parents in the day-to-day management of the diet so that the intake of calories, protein, vitamins, calcium and phenylalanine will be adequate. In case of dietary indiscretion the nutritionist's special knowledge is needed in readjusting the diet or in performing selected dietary analysis.

The social worker is helpful in family counseling, maintaining good rapport with the family, and interpreting the physician's findings to the parents. It has been our experience that the impact on parents of such a restrictive diet can interfere with management as well as create family tensions. Public health nursing is very useful to parents in the day-to-day problems of habit training, discipline and feeding routines. The nurse can also observe in the home and detect unsuspected dietary indiscretions. The role of the psychologist is self-evident. It is through the use of such additional skills[37] that a pediatrician finds himself in an optimal position to provide coordinated care for the child and his family.

Summary

The importance of early diagnosis in phenylketonuria cannot be over-emphasized. In spite of the rarity of the disease, it is of great social importance to the affected family and of economic concern to government. Optimal dietary management requires the help of the paramedical disciplines of nutrition, social work, public health nursing and psychology.

Therapeutic results are reviewed in 31 children. The best results were obtained with early diagnosis and treatment prior to 6 months of age. Caution is advised as to when dietary therapy should be discontinued.

REFERENCES

1. Folling, A: Ueber Ausscheidung von Phenylbrenztraubensaure in den Harn als Staffwechselanomalie in Verbindung mit Imbezilitaet. Ztschr. fuer Physiol. Chem., 227:169. 1934.

2. Bickel, H., Gerrard, J., and Hickmaus, E. M.: Influence of Phenylalanine Intake on Phenylketonuria. Lancet 2:812, 1963.

3. Bickel, H., Gerrard, J., and Hickmaus, E. M.: The Influence of Phenylalanine Intake on the Chemistry and Behavior of a Phenylketonuric Child. Acta Pediatrica, 43:64, 1954.

4. Woolf, L. I., Griffiths, R., and Moncrieff, A.: Treatment of Phenylketonuria with a Diet Low in Phenylalanine. British Medical Journal, 1:53, 1955.

5. Armstrong, M.D., and Tyler, F. H.: Studies on Phenylketonuria. I. Restricted Phenylalanine Intake in Phenylketonuria. Journal of Clinical Investigation 34:565, 1955.

6. Horner, F. A., and Streamer, C. W.: Effect of a Phenylalanine Restricted Diet on Patients with Phenylketonuria. Journal of the America Medical Association, 161:1629, 1956.

7. Horner, F. A., Streamer, C. W., Clader, D. E., Hassell, L. L., Binkley, E. L., and Dumars, K. W.: Effect of Phenylalanine Restricted Diet in Phenylketonuria II. American Journal of Diseases of Children, 93:615, 1957.

8. Hsia, D., Knox, W. E., Quinn, K. V., Paine, R. S.: A One-Year, Controlled Study of the Effect of Low-Phenylalanine Diet on Phenylketonuria. Pediatrics, 21:178, 1958.

9. Berry, H. K., Sutherland, B.S., Guest, G. M., and Umbarger, B.: Chemical and Clinical Observations During Treatment of Children with Phenylketonuria. Pediatrics, 21:929, 1958.

10. La Du, B. N., Editorial: The Importance of Early Diagnosis and Treatment of Phenylketonuria. Annals of Internal Medicine, 51:1427, 1959.

11. Knox, E. W.: An Evaluation of the Treatment of Phenylketonuria with Diets Low in Phenylalanine. Pediatrics, 26:1, 1960.

12. Centerwall, W. R., Centerwall, S. A., Acosta, P., and Chinnock, R. R.: Phenylketonuria I. Dietary Management of Infants and Young Children. Journal of Pediatrics, 59:93, 1961.

REFERENCES
(cont'd.)

13. Berman, P. W., Graham, F. K., Eichman, P. O., and Waisman, H. A.: Psychologic and Neurologic Status of Diet-Treated Phenylketonuric Children and Their Siblings. Pediatrics, 28:924, 1961.

14. Bickel, H., and Gruter, W.: Prophylaxe und Behandlung ther Phenylketonurie. Deutsche Med. Wohenschr., 86:39, 1961.

15. Wright, S. W.: Phenylketonuria. Journal of the American Medical Association, 165:2079, 1957.

16. Penrose, L. S.: Inheritance of Phenylpyruvic Amentia (Phenylketonuria). Lancet, 229:192, 1935.

17. Jervis, G. A.: Genetics of Phenylpyruvic Oligophrenia. Journal of Mental Science, 85:719, 1939.

18. Guthrie, R.: Blood Screening for Phenylketonuria. Journal of the American Medical Association. 1961.

19. Centerwall, C. R., Chinnock, R. F., and Pusavat, A.: Phenylketonuria: Screening Programs and Testing Methods. American Journal of Public Health 1960.

20. Gibbs, N. K., and Woolf, L. I.: Results of a One Year Programme For Its Detection in Infancy and Among Mental Defectives. British Medical Journal, 1:532, 1959.

21. Berry, H. K., Sutherland, B., and Guest, G. M.: Simple Method for the Detection of Phenylketonuria. Journal of the American Medical Association, 167:2189, 1958.

22. Wright, S. W., and Tarjan, G.: Phenylketonuria. American Journal of Diseases of Children, 93:405, 1957.

23. Jervis, G. A.: Phenylpyruvic Oligophrenia: Introductory Study of 50 Cases of Mental Deficiency Associated with Excretion of Phenylpyruvic Acid. Archives of Neurology and Psychiatry, 38:944, 1937.

24. Paine, R. S.: The Variability in Manifestations of Untreated Patients with Phenylketonuria. Pediatrics, 20:290, 1957.

25. Partington, M. W.: The Early Symptoms of Phenylketonuria. Pediatrics, 27:465, 1961.

26. Blattner, R. J.: Comments on Current Literature: Phenylketonuria: Phenylpyruvic Aciduria. Journal of Pediatrics, 59:294, 1961.

REFERENCES
(cont'd.)

27. Armstrong, M.D., and Low, N. L.: Phenylketonuria VIII. Relation Beteen Age, Serum Phenylalanine Level, and Phenylpyruvic Acid Excretion. Proceedings of the Society for Experimental Biology and Medicine, 94:142, 1957.

28. Centerwall, W. R., Centerwall, S. A., Armon, V., and Mann, L. B.: Phenylketonuria II. Results of Treatment of Infants and Young Children. A Report of 10 Cases. Journal of Pediatrics, 59:102, 1961.

29. Caudle, H.: Personal Communication. Phenylketonuria Without Mental Retardation. Pediatrics, 26:502, 1960.

30. Woolf, L. I., Ounsted, C., Lee, D., Humphrey, M., Cheshire, N. M. Humphrey, M., and Steed, G. R.: Atypical Phenylketonuria in Sisters with Normal Offspring. Lancet, 2:464, 1961.

31. Bickel, H.: Chapter in Phenylketonuria; Edited by Frank Lyman. Charles C Thomas, Springfield, Illinois, 1963.

32. H~~on~~or, F. A., et al: Termination of Dietary Treatment of Phenylketonuria. New England Journal of Medicine, 266:79, 1962.

33. Kretchmer, N., and Etzwiler, D. D.: Disorders Associated with Metabolism of Phenylalanine and Tyrosine. Pediatrics, 21:445, 1958.

34. PKU. A Diet Guide for Parents of Children with Phenylketonuria, Prepared by the Bureau of Public Health Nutrition of the California State Department of Health, 1961.

35. Shaw, K. F., Koch, R., Schild, S., Fishler, K., and Ragsdale, N.: The Team Approach to Phenylketonuria. Published by the Childrens Bureau of the Department of Health, Education, and Welfare, Washington, D. C., 1961.

36. Umbarger, B.: Phenylketonuria - Treating the Disease and Feeding the Child. American Journal of Diseases of Children, 100:908, 1960.

37. Berman, P. W., Graham, F. K., Eichman, P. L., Waisman, H. A.: Psychologic and Neurologic Status of Diet-Treated Phenylketonuric Children and Their Siblings. Pediatrics, 28:924, 1961.

FAMILY ATTITUDES AND THE LOW PHENYLALANINE DIET

By

Sylvia Schild, M.S.W.

Treatment of the child with phenylketonuria by a restrictive diet regimen has important implications for the family as well as for the health of the child. Eating is the child's earliest emotional contact and quickly equated with parental love and attention, particularly that of the mother. Very often, eating becomes the center of many problems of infants and children as they attempt to resolve difficulties engendered by parental inner conflicts, attitudes, and management directed around feeding. When certain food is withheld, the child is faced with learning new eating habits and patterns. The heightened parental anxiety and concerns about what the child eats is easily transmitted to the child. Feeding can be an anxiety-inducing situation, creating further tensions in the parent-child relationship.

The restrictive diet can be equally stressful for parents whose attitudes towards feeding reflect their own experiences and feelings about food and who have their own ideas of what and how their child should eat. The parent must guard against oversolicitousness and overemphasis on the diet, learn to withhold food from the child without feeling punitive, and must not use the diet as a weapon in dealing out other aspects of the parent-child relationship. The diet must not be allowed to dominate the family functioning completely or to a large degree, or it may affect the mental health of the family unit.

Parents need help in understanding their own attitudes about food and special diets. These feelings are often projected onto the child and interfere with successful maintenance of the diet. An understanding of the disease process dictating the dietary treatment is basic so that the parents have a sound rationale to adhere to the diet, and are realistic as to results obtainable for their child by virtue of the treatment.

The following is a brief report of the findings of a questionnaire sent to 23 families in California in 1961. These families were receiving the diet through a special PKU project at the Child Development Clinic. Seventy-eight percent of the families responded.

The average age of the child was 4, the average maternal age was 32, and the father age 34. There were 2-1/2 siblings on the average per family. In 55 percent (10 families) there were other PKU children. The average length of time that the child had been on the diet had been 23 months.

One hundred percent of the families reported they understood the diet and found no difficulty in interpreting the need for the diet to relatives and friends. Motivation to adhere to the diet was high and was demonstrated by the fact that solutions were readily found to cope with the mechanics of managing the diet. Solutions were not as satisfactorily or as easily accomplished where the problems involved inter-personal relationships within the family unit.

The motivation to sustain the diet was rewarded and reinforced by the child's improvement. It appeared from the findings on the questionnaire that with the older child, it was more difficult to supervise the obviously different dietary regimen. Families faced new problems in dietary management with different stages in the child's development. For example, in the 4 to 6 year level, when children usually leave the protective environment of the home to be out in the neighborhood or in school, parents expressed sorrow because their child could not partake of the usual childhood goodies like birthday cake and ice cream. The child in turn, responded to the differences in the diet with frustrated behavior; tantrums, pouting, whining, and yelling. Parents attempted to cope with the problem by substitution of foods which might pacify, but this did not apparently appease the parent's own feelings of being sorry for the child. They often felt unfair to the child as compared with the normal siblings.

Snitching food from the table or refrigerator was universally reported about the older child. It was speculated that the older the child, the more related the dietary management became to parental stability and their methods of coping with and disciplining the child's behavior. In the earlier years, the feeding of the PKU child simulated that of the normal child much more closely, and parents had relatively little difficulty in adhering to the prescribed diet. The child's ready dependence on the parent facilitated control of the diet by highly motivated parents despite their ambivalent feelings. As the child grew older, the parent's ambivalence became reactivated with the child's increasing independence and especially as more outsiders were becoming involved in the child's activities. Parents tended to project their own uneasy feelings about the diet onto the child and complain about the child's behavior and unhappiness with his food. It was concluded from study of the questionnaires that where the diet management was in question, it would be worthwhile to investigate not only the parental errors and confusions about diet content, but also to be keenly aware of the changes occuring in family functioning, which affect and are affected by the special diet.

With the increased caseload of patients receiving dietary treatment and medical supervision of the Child Development Clinic, it was possible to evaluate whether the preliminary findings of the questionnaire held true. In April of 1963, the caseload consisted of 30 children in 22 families who were being provided ongoing dietary therapy. In general, experience with these families has borne out the speculations made on the basis of the questionnaire study.

Parents of newborn PKU children see excellent progress and are highly motivated to keep their babies on the diet, particularly if there is an older PKU child who was not diagnosed early. When the diagnosis of phenylketonuria is made from 10 months of age and up, parents struggle with the shifting of food patterns, and their strong feelings that they are depriving their children of normal satisfactions. Almost every one of the families under care have reported problems with the child "sneaking" food. The parents need to be given considerable support that some dietary breaks will occur through no fault of their own as the child becomes more autonomous in his behavior.

The problem of diet supervision imposes much strain on the parent-child relationship. Occasionally in an effort to attain some relief, the parents tend to place or shift too much responsibility on the normal siblings, creating problems in sibling relationships. Parents require much help in understanding how the normal child uses food as an attention getting device, as a manipulative maneuver, or as a method of testing the affection of the parent. Parents of phenylketonuric children have to learn to discriminate the appropriate developmental behavior around food from behavior related to actual physiologic hunger, so as to learn what behavior is and is not due to the restrictions of the low phenylalanine diet.

In terms of the PKU child, it can generally be said that if good child-rearing practices exist in the family and if the child is well disciplined, there will be reasonably little difficulty with the dietary regimen over a long period of time. If, however, the diet is established in such a way that the child learns to use food as one way of dealing out his emotional frustrations and problems, there will be continual difficulty in maintaining adequate dietary control.

PHENYLKETONURIA: NURSING RESPONSIBILITY

Nancy Ragsdale, RN MPH

Nursing has responsibility in several areas where phenylketonuria is concerned. It has a role to play both in detection and in assisting the family to manage the dietary treatment.

Case Finding

Even in populations where the disease is not suspected, the diagnosis of phenylketonuria can be made early enough to ameliorate retardation by the application of simple screening tests to the urine. After the sixth week of life, the PKU baby will excrete abnormal metabolic compounds in his urine. Aqueous ferric chloride in a 10% solution dropped on a urine saturated diaper forms a green spot if these compounds are present. Phenistix, a chemically treated paper strip, also reacts and turns green when dipped in PKU urine or touched to the wet diaper. These tests are quite reliable, inexpensive, and are suitable for screening babies seen in well baby clinics and in doctors' offices. Application of these simple tests during the first year of life would detect most of the children with PKU early enough to institute effective treatment.

Case finding efforts are more productive in high-risk populations. These high-risk populations are found in institutions for the retarded and for the mentally ill, in training classes and special education classes for retarded children in the school system and in the parent-sponsored training classes for the retarded. Although PKU individuals identified in these populations are older and their dietary treatment less promising, it is of great importance to identify them. Older children placed on the diet do benefit: their hyperactivity, seizures, if present, and eczema will disappear. Their management is made less difficult, and the children become receptive to training efforts. In addition, when a PKU individual is identified, subsequent siblings born into his family and other young relatives will have the protection of early medical investigation and treatment. Thus, all high-risk populations should be investigated.

A special high-risk population is composed of newborn siblings of known phenylketonuric patients. Here the screening for the disease is done by blood tests performed on the day of birth and three to five days thereafter. Diagnostic responsibility is clearly medical in such cases, but the nurse needs to understand the medical procedures and be able to interpret them to the family.

Essentially, the diagnostic evaluation of the newborn consists of serum phenylalanine determinations drawn on cord blood and on blood drawn three to five days later. Between the blood tests the child is placed on milk feedings in order to insure some ingestion of phenylalanine.

After the second blood is drawn, the child is placed on a Lofenalac formula until the test results are known. Should there be a rise in the serum phenylalanine level, the disease is considered present, and the Lofenalac diet is continued. Should the levels remain normal, breast or bottle feedings are resumed. The nurse will need to be vigilant to see that, milk feedings are given between the bloods, and that milk feedings are discontinued after the second blood is drawn. The baby presumpted normal should have a third phenylalanine determination after about a 6-week trial on milk feedings.

The urine tests used as screening instruments are a responsibility usually delegated to nursing. Where PKU testing is concerned, nurses should take leadership responsibility in organizing programs for the testing of children. School nurses should investigate the children in classes for retarded and physically handicapped. Nurses in institutions for the retarded and mentally ill should know the results on every patient in the institution. Public health nurses should be sure that the screening procedures are performed in well baby clinics and in all other specialty clinics where children are seen.

This implies, of course, that nursing administrators should request from their medical administrators the standing orders permitting them to do these tests. All must plan together for a sound follow-up program which will provide to the child with a positive urine test, diagnostic services, dietary treatment and medical care, and ongoing nursing assistance with the management problems. In addition, a program for the epidemiological investigation of the extended families of positive cases must be planned from the beginning. This is particularly important when an institutionalized population is to be screened. Otherwise, families of the institutionalized patient may never be notified of the diagnosis and, ignorant of the problem, will fail to bring new infants in the family to medical attention.

The incidence of the disease is low, and one nurse may test children for years and never find one case. To test carefully for years without returns calls for a high level of professional conscientiousness on the part of the nurses. However, one has only to remember the large numbers of nurses testing, and the large numbers of children being tested, to realize that the probability of finding most of the individuals with the disease is good when all nurses test routinely.

The various tests used to screen for the disease and to monitor the diet are outlined below:

TESTS USED IN PHENYLKETONURIA

TEST	METHOD	USE
1. "Diaper test" of urine.	10% Ferric chloride dropped on freshly saturated diaper. Green spot read as positive, indicating probable phenylketonuria.	Method cheap and effective. Useful in screening large populations of infants. Not of value until baby is over six weeks of age.
2. Phenistix test of urine (produced by Ames, Co., Elkhart, Ind.).	Phenistix pressed against wet diaper or dipped in urine. Green reaction indicates probability of phenylketonuria.	Method simple and effective. More accurate than diaper test, but slightly more expensive. Useful for screening large populations of infants, children, and adults. Useful after sixth week of age.
3. Dintirophenlyhydrazine[1] test-tube test of urine.	One-half to 1 cc. of urine is placed in a test tube. Equal amount of DNPH solution is added. Immediate pale-yellow-orange reaction is negative. A gradual change to opaque bright-yellow is positive and indicates possibility of PKU.	Test cheap and accurate. More complicated than diaper test or Phenistix. Confusion may arise if urine is cloudy to begin with. Test most useful in clinical setting to confirm diaper test or phenistix.
4. Serum phenlalanine[2] test: Guthrie Method.	Test made from drops of blood placed on filter paper. Laboratory uses a bacterial inhibition assay method. Level above 8 mgs%. phenylalanine considered diagnostic of PKU.	Test can be used to detect PKU in newborn period. Useful to monitor PKU diet. Has advantage that blood easily obtained by heel or finger puncture.

TEST	METHOD	USE
5. Serum phenlalanine[3] test: LaDu-Michael method.	Test made from 5 cc. blood. Serum separated and tested for phenylalanine. Level above 8 mgs%. indicates phenylketonuria.	Test used for diagnosis and to monitor PKU diet. Test requires blood to be drawn from patients. Laboratory method difficult. Test not available in many laboratories.
6. Serum phenylalanine[4] test: fluorimetric method of McCaman and Robins.	Test made from 5 cc. of blood. Serum separated and tested for phenylalanine. Level above 8 mgs%. indicates phenylketonuria. In PKU patients on diet, level above 8-to-12 mgs%. indicates loss of dietary control.	Test used for diagnosis and to monitor PKU diet. Laboratory procedures more simple than La-Du Michael method. Test not available in many laboratories.

Nursing Assistance to the Phenylketonuric Child and His Family

It is the task of the public health nurse to assist the family of the PKU child to translate the evaluation and recommendations of the physician into effective management of both diet and child.

The nurse seeks to reinforce the teaching of the nature of the disease, to assist the family to provide good health care, and to assist the family to integrate the PKU child into their usual pattern of living.

Family members must have a good understanding of the nature of the disease and resolve some of their feelings about it before undertaking dietary management. The nurse's work with the family often begins with further interpretation, particularly of the hereditary aspects. Although the parents may receive the most careful counseling in the medical setting, they are anxious and frequently fail to absorb what they were taught or misinterpret the information. Requesting the parents to review their understanding of the problem will often elicit the areas needing clarification. Parental anxieties must be supported until they are comfortable in discussing the problem. Until they are comfortable, they cannot be receptive to further teaching. It may help to clarify thinking if the nurse can interpret the fact that the child's problem is a liver problem, not a problem of a congenital malformation of the brain. The slow development is the result of the metabolic problem, not the cause.

The dietary treatment plan should be reviewed with both parents. The father's understanding and support to the mother are vital to an effective dietary control. Both parents need to be assured that the diet will nourish the child and adequately substitute for the protein foods he may no longer have. Both need to demonstrate their ability to mix the low phenylalanine formula, to use the meal guide (prescription) and food lists and plan daily menus from them. Both should know how to calculate the daily phenylalanine intake. Demonstrations in the family kitchen, using familiar equipment and foods the child prefers, will be reassuring to the parents. The parents need to be assured that the child does not need to ingest the total amount of food prescribed and that force feeding, coaxing and refeeding are unnecessary.

Introduction of the Lofenalac formula usually presents no problem when the child is under a year or 2 years of life. Patient offering of the formula is all that is necessary. Parents need to have anticipatory guidance about the danger of commenting on taste or odor when offering the mixture. They need to be warned that diarrhea may accompany the first days on formula and that the appetite for solids will be depressed due to the richness of the formula. When the diet is introduced, the child's feeding patterns should not be changed too radically. The usual equipment, the usual textures of foods and the usual feeding routines should be maintained. Parents should not be requested to take on the additional stress of weaning or switching the child to table foods until the Lofenalac is well accepted.

When the child is older, introduction of the Lofenalac may be a problem. The mixture should be offered in small amounts at the start of every meal. All other fluids except water should be withheld. Between-meal feedings and sweet free-foods should not be offered. Gradually, the amount of the formula accepted by the child will increase. The parents need frequent reassurance that this will be so. Until adequate amounts of Lofenalac are accepted, the phenylalanine intake can be boosted to meet requirements by disguising small amounts of whole milk in the Lofenalac formula. (This can also be done when the child is ill and not eating well.) The amount to be used should be prescribed by the physician.

A very important part of the dietary management is the parents' record of the phenylalanine intake. This is usually requested of the parents for several days prior to the drawing of blood for serum phenylalanine tests. The phenylalanine intake must be correlated with the serum phenylalanine level in order to determine the correctness of the diet prescription. Without the record, under-prescription or over-prescription of the diet may occur. It is also a useful procedure when the serum phenylalanine rises above acceptable limits. Parents frequently are able to find the source of excess phenylalanine ingestion by a study of their records. In addition, this record is used by the dietitian to assess the total nutritional aspects of the diet, for a satisfactory serum phenylalanine level does not necessarily indicate a satisfactory nutritional status.

Common Management Problems

1. Anorexia.

   The child may be ill.

   The Lofenalac may be over-prescribed in protein and calories. This will depress appetite for solid foods.

   The child may be receiving too many sweet free foods.

   The serum phenylalanine level may be too low (less than 1mg%).

2. Hunger.

   The child may be under-prescribed in protein and calories.

   The child may be refusing Lofenalac: without the protein and calories it provides, the child could not be satisfied by the prescribed solids.

   The child may be refusing prescribed foods in order to have sweet free-foods.

3. Refusal of Lofenalac.

   The child may be having a normal variation in appetite. A study of the week's intake may show the amount to be adequate. (The child does not have to eat everything prescribed every day.)

   The Lofenalac may be over-prescribed: a small amount may be satisfying. Most commonly, constant refusal of Lofenalac indicates that the family is not offering the mixture consistently, nor are they withholding other beverages.

   The child may be have sensed parental anxieties about the diet and may be manipulating his parents by his refusal.

4. Refusal of solids.

   The child normally takes fewer solids once his Lofenalac intake is good. The parents may be regarding this intake as too low.

   Variations in appetite in young children are common. This may be the cause. Young children usually resist new vegetables and fruits and the parents need encouragement to continue to offer them.

   The child may be over-prescribed in Lofenalac.

   The child may be holding out for free-foods.

The child may be manipulating his parents.

5. Inappropriate feeding behavior: failure to be weaned, feed self, take solid foods, etc.

   Parental over-protection due to their emotional involvement may be the problem.

   The child may be manipulating his parents.

   On the other hand, the child may be mentally retarded, and his feeding behavior may be appropriate to his mental age, not his chronological age. He may be learning, but very slowly.

Areas of nursing instruction and assistance are dietary management, urine testing and instructions regarding the use of the medical, dietary, social and psychological services. Once dietary treatment is underway, nursing focus should move away from the disease and diet therapy to the areas of well child supervision and family health matters. To do so will help clarify a common area of confusion in the minds of the parents. Parents of the PKU child may regard the child as "sick" and they are frequently unable to distinguish between the problems related to PKU and the problems encountered in rearing any child. They may tend to relate all personality traits, all behavior and all illnesses to the diagnosis. The visits to the doctor, the psychological tests and laboratory tests and the extreme restrictiveness of the diet would reinforce this impression. The parents need to be assured frequently that as long as the diet is controlled, the child can be treated as can any healthy child.

When the child is mentally retarded, however, another area of confusion and uncertainty is opened to the parents. It is difficult to distinguish among the problems due to PKU, those usually present in child rearing, and those related to the lower mental age and slow rate of learning. To help parents sort all this out, the nurse can emphasize normal development of children and assist the parents to assess for themselves their retarded child's development, as compared with normal development. Then with some understanding of the child's expected rate of learning as defined by the psychologist (i.e. his I.Q.), as well as the present developmental level, the parents can then understand the child's behavior and set the training goals and methods reasonable for his developmental level. Nursing assistance with special training routines and techniques can then be more easily understood and utilized by the parents.

The older child started on the diet can be expected to improve in his intellectual development: the older the child at the time of the diagnosis, the slower the improvement and the more modest the improvement. However, there promises to be some improvement, and and the improvement in learning ability needs to be recognized and capitalized upon by the parents. Such a child may continue to be regarded as more retarded than he actually is - particularly if there is a behavior problem present. Parental expectations may continue to be too low and the child may fail to receive the learning experiences he needs. Here both nurse and family must work closely with the psychologist to understand the implications of the psychological testing for management goals. All older retarded children placed on the diet must have, in addition, a strict training routine in order to develop the emerging intellectual potential. Without this, the older PKU child may become quieter, but he will not achieve his maximum potential.

PKU children and their siblings require discipline to instill in them the self-control and personal responsibility needed to maintain the diet as well as to make a normal social adjustment. The nurse should early draw the parents into discussions of their child-rearing methods -- remaining out of the area of feeding, if possible. The parents should select their goals and methods of discipline, and the nurse can assist them in making their practices realistic in the light of what is known about normal growth and psychological development. The nurse stresses parental solidarity and consistency. It has been observed frequently that loss of dietary control by the parents is seldom due to lack of understanding of the dietary therapy. It is more often related to loss of control of the child by the parents. It may be that a breakdown in the parent-child relationship underlies the problem and may be the cause of lack of proper discipline. The nurse should be alert to this possibility and work closely with the other team members, particularly the social worker, so that professional investigation and assistance will be uniform and supportive to the parents.

Ultimately, the management of the problem of phenylketonuria is a parental responsibility which in time is passed on to the phenylketonuric individual himself. The nurse should guide the parents to shift the responsibility for dietary control to the child as he is able to assume part or all of the responsibility. The very young child should first learn that parental authority is final. He can then be taught to refrain from snitching, to refuse foods from other than parental sources, to learn the foods permitted on the diet, and finally, to calculate and prepare his own meals. Successful management by the parents and by the patient is related to the help given to the total family at the time of diagnosis and in the ongoing professional supervision. The total family members can utilize help with this difficult problem to learn and mature. The end product of a healthy, productive, self-disciplined adult is well worth the efforts of parents and professional personnel.

REFERENCES

1. Lyman, F.L.: Phenylketonuria. Charles C Thomas Publishers, Springfield, Illinois, 1963. 315 pp.

2. PKU, A diet Guide For Professional Personnel: Bureau of Nutrition, California State Department of Public Health, 1963

3. Davis, Louise,: PKU Testing in Older Children. Nursing Outlook, Vol. II, No. 3, March, 1963.

4. Chinque, Katherine,: The Management of Children With Phenylketonuria. Nursing Outlook, Vol. X, 328-331, May, 1962.

5. Ragsdale, Nancy; and Koch, Richard: Phenylketonuria. American Journal of Nursing (in press).

PSYCHOLOGICAL ASPECTS OF PHENYLKETONURIA

Karol Fishler, Ph.D.

In the 30 years since Fölling[1] first described phenylketonuria (PKU), no clear understanding has been gained between the relationship of the biochemical abnormality and the deficiency of intellectual function usually reflected in severe mental retardation. It is thought that an autosomal recessive gene is responsible for the inability to metabolize phenylalanine in an individual born with this condition. Accumulating evidence[2-6] supports the belief that an excess of phenylalanine circulating in the blood stream unfavorably affects the brain during early growth and subsequently leads to brain damage over a period of time. Thus, it would appear that this disorder not only interferes with psychological processes necessary for normal development of cortical activity, but if untreated usually results in irreversable damage to the brain. Within this context the psychologist's interest in phenylketonuria is chiefly in observing, measuring and recording the developmental, intellectual and behavioral aspects as related to the beneficial effects of dietary treatment or lack of it. In addition to the study of an individual affected by PKU, he may be interested in investigating the intellectual aspects of the parents who are the carriers (heterozygotes) of the defective gene, as well as other siblings or family members.

Fortunately, it is possible to prevent phenylketonuric infants from developing mental retardation provided they are detected very early in infancy and placed on a low phenylalanine diet. The sooner treatment is initiated, the better are the chances of averting significant cerebral damage. Thus, according to Centerwall[7], an infant whose treatment is started at 1 month of age may be expected to develop his full potential. When treatment is started at 2 months, mentality probably will be normal, but may lag 10 or more points behind the expected IQ level of the child. In most cases, when the treatment is delayed until the second half of the first year of life, some retardation will result. Those who are diagnosed past 1 year of age or later in life and then placed on diet may show little significant IQ improvement, and are often moderately to severely mentally retarded. Wright and Tarjan[8], who reviewed 362 cases recorded in the literature, showed that 63% had an IQ of 1-20; 32% had an IQ of 21-50; 4% had an IQ of 51-70; and only 1 had an IQ over 71. In another study, Paine[9] reviewed 106 cases of which 70% had an IQ under 20; 84% had an IQ below 30; 93% had an IQ below 40; and 98.1% had an IQ under 50. These data suggest that most of the PKU children fall within the moderate to severe range of mental retardation.

There is enough evidence available to show that the low phenylalanine diet actually mimizes or prevents further deterioration in an affected child[10-12]. The reader already has had the opportunity to review some of the measurable benefits of dietary treatment in the PKU children followed at the Child Development Clinic at Children's Hospital in Los Angeles and reported earlier in Table #I under "Pediatric Aspects of Phenylketonuria." It will suffice to state that nearly every treated child including those with relatively late age of diagnosis, showed some gains in developmental progress and improvement in their behavior. All of the treated children increased their IQ or DQ levels from 4 to 43 points for an average of 17 points. A few examples of the most dramatic gains in terms of the intellectual gains of PKU children on diet are given in Table I.

Dietary Effects

Since PKU is a genetic error of metabolism transmitted by both parents, we have investigated the levels of intellectual functioning of all the parents as well as of other normal siblings in each of the 23 families from which our PKU patients came. The findings are reported in Table II.

Obviously, both the parents and other siblings of PKU patients are of normal intelligence, although four of the mothers were found to test within borderline range and so was one of the daughters. It is interesting to note that the average IQ of the fathers compared very closely with that of their sons and falls within the bright, normal range. In contrast, the IQ's of the mothers and daughters are also comparable, but slightly lower.

Emotional-Social Aspects

Although mental retardation occurs in nearly all persons affected by untreated phenylketonuria, the clinical picture varies. The PKU child is typically hyperactive and his behavior is characterized by unpredictable erratic activity. Excessive rocking movements, arm waving, teeth grinding, and overall aimless behavior sometimes suggest autism or childhood schizophrenia. In the cases with severe mental retardation, there is significant limitation in verbal communication, and vocalization may be unintelligible. Bizarre displays of motor activities, poor coordination, and difficulty in visual-perceptual areas are sometimes aggravated by the presence of convulsive disorders of the petit mal variety. These usually can be controlled by the low phenylalanine diet. Untreated children are irritable, distractible, and generally exhibit a low frustration tolerance. They do not relate well in interpersonal contacts either within their own family's structure or with strangers. Emotionally and socially they present a picture of very immature and overly-dependent youngsters. In this respect, the three R's used with other groups of mentally retarded children: Routine, Repetition, and Relaxation seem to be appropriate in helping them gain a more satisfactory environmental adjustment.

TABLE I

GAINS OF 20 OR MORE DQ/IQ POINTS

Age Dx.	Initial DQ/IQ	Diet Duration	Last DQ/IQ	DQ/IQ Gain
0-7	37	1-1	73	36
1-1	31	2-6	52	21
1-2	40	5-1	68	28
1-6	49	1-4	86	37
1-6	46	1-8	69	23
2-8	43	3-10	76	33
3-3	10	3-8	53	43

TABLE II

DISTRIBUTION OF IQ LEVELS IN PARENTS AND UNAFFECTED SIBLINGS OF PKU PATIENTS

Fathers (N = 22*)		Mothers (N = 23)	
Range:	IQ 89 - 130	Range:	IQ 72 - 130
Mean:	IQ 112.4	Mean:	IQ 103.2
Sons (N = 11)		Daughters (N = 10)	
Range:	IQ 94 - 126	Range:	IQ 78** - 128
Mean:	IQ 113.2	Mean:	IQ 102.6

* One father is separated and not available for testing.

** Sibling with IQ 78 has parents with following IQ's:
Father: IQ 97 - Mother: IQ 72.

Summary

In spite of the rarity of PKU, early diagnosis is of utmost importance. Our own findings based on a sample of 33 PKU children who were treated with a low phenylalanine diet substantiate earlier impressions postulated by Centerwall. Thus, the sooner the child is diagnosed and started on therapy, the better his chances for a normal or near normal mental development. This is especially true if the child with PKU is identified within the first 6 months of life. Those diagnosed from 6 to 12 months of age are often within borderline or mild retardation range and those identified after 1 year of life or later are frequently mildly to severely mentally retarded. Regardless of when treatment is initiated, its beneficial effect is almost universally manifested in behavioral improvement of the child, even though the intellectual gains may be minimal.

The role of the psychologist is limited chiefly to periodic evaluations of a PKU child with regard to his mental development. It is obvious that psychologists do not yet have a complete understanding of the dynamics involved. The degree of mental retardation and the subsequent improvement derived from dietary treatment shift the emphasis more onto the physical management of the child than rehabilitation in terms of personality changes through conventional psychotherapy to enhance emotional growth and stability in such children. It is evident that repeated psychometric evaluations of a PKU child on a longitudinal basis are necessary to observe mental progress in order to plan realistically for the child and his family.

REFERENCES

1. Fölling, A.: Uber Ausscheidung von Phenylbrenztraubensaure in den Harn als Staffwechselanomalie in Verbindung mit Imbesillitat. Ztschr. f physiol. Chem., 227:169, 1934.

2. Hsia, D., Knox, W.E., Quinn, K.V., and Paine, R.S.: A One Year, Controlled Study of the Effects of Low-Phenylalanine Diet on Phenylketonuria. Pediatrics, 21:178, 1958.

3. Woolf, L.J., Griffiths, R., Moncrieff, A., Coates, S., and Dillistone, F.: The Dietary Treatment of Phenylketonuria. American Journal of Disease of Children, 33:31, 1958.

4. Jervis, G.A.: Metabolic Defects Affecting the Central Nervous System in the The Effect of Pharmacologic Agents on the Nervous System, Vol. 37, Baltimore, Williams & Wilkins, 1959.

5. Horner, F.A., and Streamer, C.W.: Phenylketonuria Treated from Earliest Infancy. American Journal of Diseases of Children, 97:345, 1959.

6. Coates, S.: Results of Treatment of Phenylketonuria. British Journal of Medicine, 1:767, 1961.

7. Centerwall, W.R., Chinnook, R.F., and Pusavat, A.: Phenylketonuria: Screening Programs and Testing Methods. American Journal of Public Health, 50:11, 1960.

8. Wright, S.W., Tarjan, G., Lippman, R.W., and Perry, T.L. Etiologic Factors in Mental Deficiency. American Journal of Diseases of Children, 95:541, 1958.

9. Paine, R.S.: The Variability in Manifestations of Untreated Patients with Phenylketonuria. Pediatrics, 20:290, 1957.

10. Knox, E.W.: An Evaluation of the Treatment of Phenylketonuria with Diets Low in Phenylalanine. Pediatrics, 26:1, 1960.

11. Centerwall, W.R., Centerwall, S.A., Armon, V., and Mann, L.B.: Phenylketonuria II: Results of Treatment of Infants and Young Children: A Report of 10 Cases. Pediatrics, 59:102, 1961.

12. Bickel, H.: Phenylketonuria. Edited by F. Lyman. Charles C Thomas, Springfield, Illinois, 1963.

NUTRITIONAL ASPECTS OF PHENYLKETONURIA

Phyllis B. Acosta, M.S.

Treatment of the herediatary metabolic diseases elicits a great deal of teamwork among members of the medical profession. In treating a patient with phenylketonuria, for instance, we find the physician, biochemist, nutritionist or dietitian, psychologist and nurse working hand in hand. It is possible for the practicing physician to treat these metabolic disorders alone if he is willing to spend some time in learning food values and basic nutrient requirements in relation to the disease involved, but with such a group of specialists available, the physician makes his work easier and more accurate by calling on specially trained individuals for help.

Development of Treatment

Since the discovery of phenylketonuria (PKU) in 1934, various methods of treatment have been used without success. Amino acids (21,26,31), vitamins (20), hormones (10,28), and blood transfusions (19) have been tried with poor results. Bickel and co-workers (5) in England in 1952 were the first to try a diet low in phenylalanine for the treatment of a 2 year old PKU child with good results. Since that time, many glowing reports have appeared to substantiate their findings (2-4,6,13 15,30). With the efficacy of dietary treatment established, the next step has been to provide simple methods of calculation and preparation for the mother who is faced with serving three or more meals a day for her PKU child.

While it is true that good results may be obtained by early treatment of the PKU child with a diet restricted in phenylalanine (16,17), the diet may of itself present problems. Most natural proteins contain 4 to 6% phenylalanine (3). This makes it impossible to prepare a well-balanced diet which supplies all the necessary nutrients from natural foods. A casein hydrolysate (Lofenalac) with 95% of the phenylalanine removed has been prepared as the basis for a phenylalanine-restricted diet. This hydrolysate has fat, carbohydrate, and some vitamins and minerals added. It is proving to be an excellent substitute for milk and other foods high in protein. Any child, however, needs more than a liquid formula to grow and develop normally.

Lyman first devised an "equivalent" list of foods with 1 equivalent equal to 15 mg. of phenylalanine (18,24). Later, serving lists were evolved in order to give the parents a simple outline for the diet of their child (1). The serving lists are based on the same principles as are those of the diabetic exchange lists; that is, foods with similar nutrient value (protein, phenylalanine, carbohydrate) are placed in the same list. However, the amounts of food differ in order that the nutrients may remain constant. The lists, with the phenylalanine, protein, and caloric content are given in table I. Food items in these lists are shown in table II.

These serving lists are presently in use in several medical centers in California.

Importance of Balanced Diet

Umbarger (29), in a very excellent paper, has stressed the need for establishment of normal attitudes toward food. The need for normal food habits and a well balanced diet are also important. The nutritionist must be aware of the nutrient needs of the normal infant and child in order to properly teach good nutrition to parents of the child with phenylketonuria. Various nutrient needs of the PKU child will be discussed in relation to the needs of the normal child of the same age.

Phenylalanine. The approximate phenylalanine requirements of the normal and PKU child are given in table III. Studies of amino acid requirements of normal children between the ages of 9 months (27) to 12 or 13 years of age are lacking. However, the phenylalanine requirement of the normal infant from 1 to 9 months of age appears to be approximately 41 mg. per lb. (27). According to Centerwall and co-workers (9), there is a gradual decline in the phenylalanine requirement of the PKU child with increasing age. They set as an approximate range for a base line in beginning treatment a high of 22 mg. per lb. at birth with a gradual decrease to approximately 10 mg. per lb. at 7 years of age. See table III for the ranges within various groups. Emphasis should be placed on the fact that these figures are tentative and may need to be increased or decreased depending on the tolerance of the child being treated. Paine and Hsia (23) have indicated that the tolerance of one 6 month old PKU child appeared to be 11 mg. per lb. which is much lower than the range set for this age by Centerwall.

Protein. The actual protein requirements of infants and children are still much in question. Therefore, in table III the protein recommended is based on the Allowances of the National Research Council for the artifically fed infant (25). In current practice, diets furnishing 1.6 gm. of protein and more per pound are in common use. Since the protein for these PKU children is in the form of a casein hydrolysate, it may be necessary to give more protein than the normal amounts. From birth to 7 years of age, there is a possible decrease in requirements from 1.6 gm. protein per lb. to approximately 1.3 gm. protein per pound of normal body weight. The diets included in this paper contain more than the National Research Council Recommended Allowances for early infancy.

TABLE I

Phenylalanine, Protein, and Caloric Content of Serving Lists Used on Restricted Phenylalanine Diets

	PHENYLALANINE	PROTEIN	CALORIES
	Mg.	Gm.	
Vegetables	15	0.3	5
Fruits	15	0.2	80
Breads	30	0.5	20
Fats	5	0.1	45
Desserts*	30**	2.0**	270**
Free Foods	0	0.0	Varies

*Special recipes must be used.
**Averages from all dessert recipes.

TABLE II

Serving Lists for Phenylalanine Restricted Diet

VEGETABLES

Each serving as listed contains 15 milligrams of phenylalanine

Baby and Junior Vegetables

Beans, green, strained and junior	2 Tbsp.
Beets, strained	2 Tbsp.
Carrots, strained and junior	3 Tbsp.
Spinach, creamed, strained and junior	2 Tbsp.
Squash, winter, strained	3 Tbsp.
junior	6 Tbsp.
Tomato juice	2 Tbsp.
Yam or sweet potato, strained	2 Tbsp.

Table Vegetables

Asparagus	1 Stalk
Beans, green, cooked	3 Tbsp.
Beets, cooked	3 Tbsp.
Cabbage, raw, shredded	4 Tbsp.
Carrots, raw	1/2 Large
canned	4 Tbsp.

TABLE II (Continued)

Cauliflower	2 Tbsp.
Celery, raw (5 in. long stalks)	2 Stalks
Cucumber, raw	1/3 Med.
Lettuce, head	2 Leaves
Mushrooms, cooked	2 Tbsp.
Okra, pod, cooked	1 Pod
Onion, mature	1/4 Med.
green	2 Med.
Parsley	2 Sprigs
Pumpkin, cooked	2 Tbsp.
Radish, small, raw	3 Small
Spinach, cooked	1 Tbsp.
Squash, winter, cooked	2 Tbsp.
summer, cooked	4 Tbsp.
Zucchini, cooked	4 Tbsp.
Tomato, raw	1/4 Small
canned	2 Tbsp.
juice	2 Tbsp.
Turnip	4 Tbsp.

FRUITS

Each serving as listed contains 15 milligrams of phenylalanine

Baby and Junior Fruits

Apricot-applesauce, strained and junior	10 Tbsp.
Banana	4 Tbsp.
Orange juice	3 Tbsp.
Peaches, strained	5 Tbsp.
junior	7 Tbsp.
Pears, strained and junior	10 Tbsp.
Pear-pineapple, strained and junior	7 Tbsp.
Plums with tapioca, strained	5 Tbsp.
junior	7 Tbsp.
Prunes, strained	3 Tbsp.

Table Fruits

Apple, raw	1 Small
Apricots, canned	2 Halves
juice	1/4 Cup
Avocado	2 Tbsp.
Banana	4 Tbsp.
Dates, dried	2
Cantaloupe, small	1/8 Melon
Fruit cocktail, canned	2 Tbsp.
Grapefruit, sections or juice	1/3 Cup
Grapes, green, seedless	20 Med.
Guava, raw	1/3 Med.

Grape juice	1/3 Cup
Lemon or lime juice	3 Tbsp.
frozen concentrate, mixed	1/2 Cup
Mango	1/2 Small
Orange, sections or juice	3 Tbsp.
Papaya juice	1/2 Cup
Papaya, cubed	1/4 Cup
Peaches, raw	2/3 Med.
canned in syrup	1-1/2 Halves
Pear, raw	1/3 Med.
canned in syrup	3 Halves
Pineapple, raw	1/3 Cup
canned in syrup	1-1/2 Sm. Sl.
juice	1/2 Cup
Plums, canned in syrup	1 Med.
Popsicle with fruit juice	1
Prunes, cooked	2 Med.
juice	1/3 Cup
Raisins	1 Tbsp.
Strawberries	3 Large
Tangerine	2/3 Small
Watermelon	1/3 Cup

BREAD, CEREALS

Each serving as listed contains 30 milligrams of phenylalanine

Baby Foods	
Barley cereal, Gerber's, dry	2 Tbsp.
Cereal food, Gerber's, dry	2 Tbsp.
Mixed cereal, Pablum, dry	3 Tbsp.
Oatmeal, Gerber's strained	2 Tbsp.
Pablum, dry	2 Tbsp.
Rice Pablum	4 Tbsp.
Table Foods	
Biscuits*	1 Small
Corn, cooked	2 Tbsp.
Cornflakes	1/3 Cup
Crackers, Barnum animal	6
Crackers, graham	1
Crackers, soda	1
Crackers, saltines	2
Cream of Rice, cooked	2 Tbsp.
Cream of Wheat, cooked	2 Tbsp.
Hominy	3 Tbsp.

*Low phenylalanine recipes.

TABLE II (Continued

Hominy grits, cooked	3 Tbsp.
Muffin, pineapple*	2
Popcorn	1/3 c., popped
Potato, Irish	2 Tbsp.
Rice, cooked	2 Tbsp.
Rice Flakes, Quaker	1/3 Cup
Rice Krispies, Kelloggs	1/3 Cup
Rice, Puffed, Quaker	1/3 Cup
Sugar Crisps	1/4 Cup
Wheat, Puffed, Quaker	1/3 Cup
Yam, sweet potato, cooked	2 Tbsp.

FATS

Each serving as listed contains 5 milligrams of phenylalanine

Cream, heavy	1 Tsp.
Mayonnaise	2 Tsp.
Olives, ripe	1 Large

DESSERTS

Each serving as listed contains 30 milligrams of phenylalanine

Cake*	1/12 of cake
Cookies--Rice flour*	2
Corn starch*	2
Cookies, Arrowroot	1-1/2
Ice Cream--Chocolate*	2/3 Cup
Pineapple*	2/3 Cup
Strawberry*	2/3 Cup
Jello	1/3 Cup
Puddings*	1/2 Cup
Sauce, Hershey	2 Tbsp.
Wafers, sugar, Nabisco	6

FREE FOODS

Each serving as listed contains little or no phenylalanine
May be used as desired

Apple juice) If more than a cup,
Applesauce) count as a fruit
Butter

Gingerbread*
Guava butter
Honey

*Low phenylalanine recipes.

TABLE II (Continued)

- Candy
  - butterscotch
  - cream mints
  - fondant
  - gum drops
  - hard
  - jelly beans
  - lollipops
- Cornstarch
- Sauces*
  - lemon
  - white
- Jams, jellies, marmalades
- Margarine
- Molasses
- Oil
- Pepper
- Popsicle (with fruit flavoring only)
- Rich's Topping
- Salt

- Sugar, brown or white
- Syrups, corn, maple
- Tapioca

FOODS TO AVOID

Each serving is very high in phenylalanine
May not be used except with physician's permission

- Breads
- Cheese, all kinds
- Eggs
- Flour, all kinds
- Meat, poultry, fish
- Legumes (dried peas, beans and seeds)
- Nuts
- Nut butters
- Milk (55 milligrams phenylalanine per ounce)

---

*Low phenylalanine recipes.

Fat. Presently there are no set requirements for fat in the diet. However, recent research points to the possibility that better growth may be obtained on fewer calories if some saturated fat is included (12). The casein hydrolysate contains only unsaturated fat. Perhaps in the future, more attention can be given to this aspect of the diet.

Carbohydrate. Blainey and Guilliford (6) state that high carbohydrate diets are essential in the treatment of children with phenylketonuria on restricted phenylalanine intakes. They propose that 70% of the total calories should be in the form of carbohydrates.

Calories. The caloric requirements set for the normal child in table III are based on NRC Recommended Dietary Allowances (25). These requirements (for the normal child) decrease from approximately 55 calories per lb. at birth to approximately 40 calories per lb. at 7 years of age. The caloric requirements of the PKU child, according to some investigators (6,9), appear to be higher. Centerwall et al. (9), suggest 60-65 calories per pound for the newborn PKU infant. At 7 years of age children with this disease should receive 40-50 calories per pound. However, it now appears that those PKU children treated from birth may not require additional calories, but that the NRC Recommended Daily Dietary Allowances are adequate when hyperactivity is not present.

Calcium. There is little need for concern over meeting calcium needs of infants and children on the low phenylalanine diet if the National Research Council Recommended Dietary Allowances for protein are met by the use of Lofenalac. However, calcium deficiency may occur in older children who are not obtaining sufficient amounts of protein because of lack of funds to purchase the hydrolysate. (11) For these children, the physician should give serious consideration to supplementing the diet with calcium since there have been known cases of calcium deficiency with resultant tetany.

Vitamins. The vitamins usually prescribed for the normal young infant may well be given to the PKU child in the early months of life. However, as the child's food is changed and more vegetables and fruits are added, possibly the only vitamin needing supplementation is niacin. In those children receiving large amounts of vegetables, there is a possibility of the occurrence of carotenemia (11). Care should be taken in the selection of vegetables so that those contining large amounts of carotene are not continually used.

If proper attention is not given to the protein requirements, there will be a definite need for niacin supplementation since tryptophane may not be present in sufficient amounts for conversion to niacin (11). Supplementation with other B vitamins does not appear necessary when a properly planned diet is given (11).

TABLE III

Phenylalanine, Protein, and Calories
Recommended for Various Age Groups

AGE	PHENYLALANINE		PROTEIN (25)		CALORIES/LB.	
	Mg. per lb. (9)		Gm. per lb.		(25)	(9)
	Normal	PKU	Normal	PKU	Normal	PKU
0-3 Months	1-9 Mo. (27) 41	20-22	2-6 Mo. 1.1-1.6	$1\frac{3}{4}$-2	2 Mo. 55	60-65
4-12 Months		18-20 11 (23)	7-12 Mo. .9-1.4	$1\frac{1}{2}$	7-12 Mo. 45	55-60
1-3 Years	*	16-18	1.5 (40 gm. total)	40 gm. total	43-48 (1300 total)	50-55
4-7 Years	*	10-16	1.3 (50 gm. total)	50 gm. total	42 (1700 total)	40-50

*No research on requirements for this age.

Calculation of Diets and Sample Menus

The dietitian, nutritionist, or nurse, when planning a diet for a phenylketonuric child should have a definite prescription from the child's physician. This prescription should at least contain the desired amount of phenylalanine and total number of calories for the day. Preferably the diet prescription would also contain the amount of protein desired. The phenylalanine restricted diet can readily be calculated from a clear prescription. However, it should be kept in mind that the prescription is based on blood and urinalyses which indicate individual tolerances. Although averages may be given for various ages, these should be used as base lines for beginning treatment. Each child is an individual and must be treated individually. Also, food likes and dislikes must be taken into consideration if the diet is to succeed. The following outline may be of value in prescribing and calculating a low phenylalanine diet.

Prescription and Calculation of the Low Phenylalanine Diet[1]

1. Establish the child's daily requirements for phenylalanine, protein, and calories according to his age. Write the diet prescription to include the amounts of all three. Average requirements by age are listed in Table III.

2. Establish the amount of Lofenalac to be given. The amount of Lofenalac to be prescribed as determined by the total protein requirement of the child. From 100 percent to 85 percent of the total protein need of the child must be met by the Lofenalac, as natural foods necessary to meet this need would be too high in phenylalanine. (See Table IV.)

   A. Newborn period to age of introduction of solids:
   During the period before the infant can eat solid food, the Lofenalac is his only source of protein. Since Lofenalac does not contain enough phenylalanine to supply the infant's need for growth during this age period, whole milk should be added to the Lofenalac, making a mixture which will contain the amount of phenylalanine needed to maintain normal serum phenylalanine levels. One to 2 ounces of whole milk are added to the Lofenalac mixture on the basis that one ounce of whole milk supplies 55 milligrams of phenylalanine, 1.1 grams of protein, and 20 calories. The milk should always be mixed with the Lofenalac so that the child does not acquire a liking for the taste of milk

---

[1] State of California, Department of Public Health. The Low Phenylaline Diet For Professional Use Berkeley, California State Printing Office, 1963.

B. 4 to 12 months:
Ninety-five percent of the total protein should be derived from the Lofenalac. Less whole milk is necessary during this period, usually from one-half to one ounce daily. The Lofenalac, whole milk, and solids should contain enough phenylalanine to maintain normal serum phenylalanine levels. (See Table IV.)

C. 1 year to 3 years:
Ninety percent of the total protein is derived from the Lofenalac. Milk is not included in the prescription. It can be used to raise the phenylalanine intake to the prescribed amount when the child is ill or not eating well. (See Table IV.)

D. 4 to 7 years.
Eighty-five percent of the total protein is to be derived from the Lofenalac. (See Table IV.)

TABLE IV

SUGGESTED AMOUNTS OF LOFENALAC AND MILK FOR PHENYLKETONURIC INFANTS AND CHILDREN OF VARIOUS AGES

Age	Suggested protein	Percentage from Lofenalac	Lofenalac	Milk
0-3 Months	1-3/4-2 gm./lb.*	100	1¼ meas./lb.*	1-1½ oz.**
4-12 Months	1½ gm./lb.*	95	1 meas./lb.*	½-1 oz.**
1-3 Years	40 gm.	90	24 measures	none
4-7 Years	50 gm.	85	28 measures	none

*Body weight.
**55 mg. phenylalanine/oz. whole milk.

3. State the amount of Lofenalac to be given in measures or in household measuring cup terms. (See Table V.)

4. State the amount of water to be used to mix the Lofenalac powder, State it as: "Water to make ________ ounces."
The amount of water to be used is determined by the average fluid intake for the child's age, the child's preference for fluids, and his taste for Lofenalac. It should not be over

32 fluid ounces daily. In young children the ratio of Lofenalac to water is usually one measure to two ounces of water.

5. State the amount, if any, of whole milk to be added. (See Table IV.)

6. List the phenylalanine, protein, and calories that are received in the Lofenalac mixture. (See Table V.)
   Solid foods permitted on the diet may be introduced at the usual ages in the usual textures. (See Table VI.)

7. Subtract the phenylalanine allotment in the Lofenalac mixture from the total phenylalanine prescription. The difference shows the amount of phenylalanine to be given in solid foods. The solids should be prescribed in numbers of servings to take up the remaining allowance of phenylalanine, protein, and calories. The servings of solid foods prescribed should give a variety of foods and food textures. (See Tables I and II.)
   For the young child, foods to be chewed should be introduced at the usual time. Lofenalac should be offered by cup at nine months. Fats should not be added until after age one, as the Lofenalac contains adequate fat and additional fat may cause diarrhea.
   For the young child, prescribe the servings in three meals with two to three in-between feedings; for the older child, prescribe the servings in three meals.

8. Calculate the phenylalanine, protein, and calories in servings of the solid foods and add to the food value total derived from the Lofenalac. (See Table I.)

TABLE V

PHENYLALANINE, PROTEIN, AND CALORIES SUPPLIED BY VARIOUS AMOUNTS OF LOFENALAC

Measures of Lofenalac*	Phenylalanine mg.	Protein gm.	Calories
1	7.5	1.5	43
10	75.0	15.0	430
11	82.5	16.5	473
12	90.0	18.0	516
13	97.5	19.5	559
14	105.0	21.0	602
15	112.5	22.5	645
16	120.0	24.0	688
17	127.5	25.5	731
18	135.0	27.0	774
19	142.5	28.5	817
20	150.0	30.0	860
21	157.5	31.5	903
22	165.0	33.0	946
23	172.5	34.5	989
24	180.0	36.0	1032
25	187.5	37.5	1075
26	195.0	39.0	1118
27	202.5	40.5	1161
28	210.0	42.0	1204
29	217.5	43.5	1247
30	225.0	45.0	1290

*1 Measure equals 1 tablespoon.
16 Measures equal 1 cup.

TABLE VI

TIMETABLE FOR SOLID FOODS

Ages at which various food and vitamins are introduced

AGE	Vitamin D	Vitamin C	Orange Juice	Ripe Banana	Vegetables Sieved or Mashed	Fruit Puree	Special Cereal and Breads	Coarsely Chopped Foods	Special Desserts	Raw Fruit and Vegetables
2 Weeks	Begin									
3 Weeks		Begin								
1 Month			Begin							
6-8 Weeks				Begin						
10-12 Weeks					Begin					
3 Months						Begin				
5-8 Months							Begin			
9 Months*								Begin		
10 Months									Begin	
15-18 Months										Begin

* Cup feeding should be introduced at 9-12 months of age.

Four diet prescriptions for various ages are given in table VII. These prescriptions are then translated to total day's food in exchanges. Actual menus for one day are also included in table VIII.

Approximation of Phenylalanine Content

There are several publications available giving the amino acid content of various foods (7,22). However, since different methods are used in amino acid analyses, all do not agree on exact amounts of certain amino acids present. Moreover, many foods have not yet been analyzed for amino acids. Due to these factors, it has seemed expedient to use the approximate percentage of phenylalanine in food protein, 4-6%, for calculating amounts present in foods. If one takes the median or 5% of the total protein as the amount of phenylalanine present, the approximate number of milligrams can be easily calculated. As an example of this easy method of calculation, applesauce with a protein content of .3 gm. per 1/2 cup (8) may be used as follows:

1 gm. = 1000 mg.

.3 x 1000 = 300 milligrams protein

300 x .05 = 15 mg. phenylalanine

Any food which has a known protein content may be just as simply calculated. This method is particularly useful in areas where analyses for phenylalanine are lacking.

Summary

The development of a satisfactory treatment for phenylketonuria has been discussed. Phenylalanine, protein, and caloric content of the phenylalanine serving lists are given. The nutrient needs of the phenylketonuric child in relation to the needs of the normal child are discussed. Stress is placed on the importance of well-balanced diet in the treatment of PKU children. Suggestions for calculation of phenylalanine restricted diets are made and sample diets for various ages are included. A simple method of calculation of phenylalanine based on protein content is given.

TABLE VII

RESTRICTED PHENYLALANINE DIETS FOR DIFFERENT AGE INFANTS AND CHILDREN

Age	1 Month	8 Months	2 Years	4 Years
Approximate Weight in Pounds	8 lbs.	18 lbs.	26 lbs.	36 lbs.
Diet Prescription				
Phenylalanine, mg.	160-176	324-360	416-468	360-576
Protein, gm.	14-16	27	40	50
Calories	440	810	1300	1700
Lofenalac	10 ms.	18 ms.	24 ms.	28 ms.
Water	to make 24 oz.	to make 32 oz.	to make 24 oz.	to make 24 oz.
Milk as necessary	1½ oz.	1 oz.	---	---
Vegetables	---	2 serv.	4 serv.	4 serv.
Fruits	1 serv.	1 serv.	4 serv.	4 serv.
Breads	---	3 serv.	4 serv.	4 serv.
Fats	---	---	1 serv.	1 serv.
Desserts*	---	---	---	1 serv.
Free Foods**	---	---	as desired	as desired
Total from Diets				
Phenylalanine, mg.	172	325	425	485
Protein, gm.	16.8	30.4	40.1	48.1
Calories	540	944	1497	1939

* Special recipes must be used.

**If given in excessive amounts, child may not consume proper amounts of other foods.

TABLE VIII

Restricted Phenylalanine Diets for Different Age
Infants and Children

AGE	BREAKFAST	DINNER	Mid-Afternoon	SUPPER	Bedtime
8 Months	6 T. strained Oatmeal 8 oz. Formula	3 T. Jr. Carrots 8 oz. Formula	---	2 T. Jr. Green Beans 7 T. Jr. Peaches 8 oz. Formula	8 oz. Formula
2 Years	2/3 cup (2 serv.) Rice Krispies 3 oz. (6 T.) orange juice 4 oz. Formula	2 T. Mashed Potatoes, no milk, no butter 4 T. cooked carrots 1½ Sl. cnd. Pinneapple 6 oz. Formula	2 Saltines 8 oz. Formula	3 T. Cooked Green Beans ½ Sm. Raw Tomato (2 serv.) with 2 t. mayonnaise 1½ Halves cnd. Peaches 6 oz. Formula	
4 Years	2/3 cup (2 serv.) Puffed Wheat 6 T. (2 serv.) Orange sections 8 oz. Formula	2 T. Cooked corn 4 T. Cooked Summer Squash ¼ Small Tomato 2/3 cup Watermelon 8 oz. Formula	¼ cup Pudding*	2 T. Mashed Yams 4 T. Sl. Banana 2 T. Cooked Cauliflower 4 T. Shredded Raw Cabbage with 2 tsp. Mayonnaise 8 oz. Formula	

*Special recipe.

References

1. Acosta, P. B., W. R. Centerwall. "Phenylketonuria: Dietary Management--Special Low Phenylalanine Recipes," Journal of American Dietetic Association, 36:206, 1960.

2. Armstrong, M. D., N. L. Low, J. F. Bosma. "Studies on Phenylketonuria. VIII. Further observations on the Effect of Phenylalanine-Restricted Diet on Patients with Phenylketonuria," Amer. J. Clin. Nut., 5:543, 1957.

3. Armstrong, M.D., F. H. Tyler. "Studies on Phenylketonuria. I. Restricted Phenylalanine Intake in Phenylketonuria," J. Clin. Invest., 34:565, 1955.

4. Bickel, H. "The Effects of a Phenylalanine-Free and Phenylalanine-Poor Diet in Phenylpyruvic Ologophrenia," Exper. Med. & Surg., 12:114, 1954.

5. Bickel, H., J. Gerrand, E. M. Hickmans. "Influence of Phenylalanine Intake on Phenylketonuria," Lancet, 2:812, 1953.

6. Blainey, J. D., R. Gulliford. "Phenylalanine-Restricted Diets in the Treatment of Phenylketonuria," Arch. Dis. Child., 31:452, 1956.

7. Block, R. J., K. W. Weiss. Amino Acid Handbook. Methods and Results of Protein Analysis. Springfield: Charles C. Thomas, 1956, pp. 386.

8. Bowes, A. DeP., C. F. Church. Food Values of Portions Commonly Used. Eighth edition. Philadelphia: College Offset Press, 1956.

9. Centerwall, W. R., S. A. Centerwall, P. B. Acosta, R. F. Chinnock. "Phenylketonuria. I. Dietary Management of Infants and Young Children," J. of Pediatrics, 59:93, 1961.

10. Fois, A. "Current Possibilities in Therapy in Phenylpyruvic Oligophrenia," Minerva Pediat., 12:929, 1960.

11. Hartman, C. M. "The Effect of a Low Phenylalanine Diet on the Behavior of Older Phenylketonurics," Thesis in Partial Fulfillment of Requirements of Master of Science in Foods and Nutrition, College of Medical Evangelists, Los Angeles, 1961.

12. Holt, L. E., Jr. "Dietary Fat. Its Role in Nutrition and Human Requirement," J. Amer. Med. Assn., 164:1890, 1957.

13. Horner, F. A., C. W. Streamer. "Effect of a Phenylalanine Restricted Diet on Patients with Phenylketonuria. Clinical Observations in 3 Cases," *J. Amer. Med. Assn.*, 161:1628, 1956.

14. Horner, F. A., C. W. Streamer, D. E. Clader, L. L. Hassell, E. L. Binkley, Jr., K. W. Dumars, Jr. "Effect of a Phenylalanine-Restricted Diet in Phenylketonuria," *Amer. J. Dis. Child.*, 93:615, 1957.

15. Hsia, D. Y. Y., W. E. Knox, K. V. Quinn, R. S. Paine. "A One-Year Controlled Study of the Effect of a Low Phenylalanine Diet on Phenylketonuria," *Pediatrics*, 21:178, 1958.

16. Knox, W. E. "An Evaluation of the Treatment of Phenylketonuria with Diets Low in Phenylalanine," *Pediatrics*, 26:1, 1960.

17. La Du, B. N. "The Importance of Early Diagnosis and Treatment of Phenylketonuria," *Annals of Internal Medicine*, 51:1427, 1959.

18. Lyman, F. L., J. K. Lyman. "Dietary Management of Phenylketonuria with Lofenalac," *Arch. Pediatrics*, New York, 77:212, 1960.

19. Mautner, H. V. "The Ineffectiveness of Blood Transfusions on the Phenylalanine Level in Phenylketonuria. (Clinical Observation)" *Journal of the Maine Medical Association*, 51:186, 1960.

20. McGear, E. G., B. Tischler. "Vitamin B_6 and Mental Deficiency; The Effects of Large Doses of B_6 (Pyridoxine) in Phenylketonuria," *Canadian Journal of Biochemistry and Physiology*, 37:485, 1959.

21. Meister, A., S. Udenfriend, S. P. Bessman. "Diminished Phenylketonuria in Phenylpyruvic Oligophrenia After Administration of L-Glutamine, L-Glutamate or L-Asparagine," *J. Clin. Invest.*, 35:619, 1956.

22. Orr, M. L., B. K. Watt. *Amino Acid Content of Foods*. Home Economics Research Report No. 4, USDA, 1957.

23. Paine, R. S., D. Y. Y. Hsia. "Dietary Phenylalanine Requirements and Tolerance of Phenylketonuric Patients," *Amer. J. Dis. Child.*, 94:224, 1957.

24. *Phenylketonuria*: Low Phenylalanine Dietary Management with Lofenalac. Evansville: Mead Johnson and Company, 1958.

25. *Recommended Dietary Allowances*, Revised 1958. Publication 589, National Academy of Sciences - National Research Council, Washington, D.C.

26. Snyderman, S. E., P. Norton, L. E. Holt, Jr. "Effect of Tyrosine Administration in Phenylketonuria," Fed. Proc., 14:1458, 1955.

27. Snyderman, S. E., E. L. Pratt, M. W. Cheung, P. Norton, L. E. Holt, Jr., A. E. Hanson, T. C. Panos. "The Phenylalanine Requirement of the Normal Infant," J. Nut., 56:253, 1955.

28. Thelander, H. E. "Observations on the Effect of Cortisone in a Case of Phenylpyruvic Oliogophrenia," Calif. Med., 89:359, 1958.

29. Umbarger, B. "Phenylketonuria - Treating the Disease and Feeding the Child," AMA J. Dis. Child., 100:908, 1960.

30. Woolf, L. I., R. Griffiths, A. Moncrieff. "Treatment of Phenylketonuria with a Diet Low in Phenylalanine," British Journal of Medicine, 1:57, 1955.

31. Woolf, L. I., D. G. Vulliamy. "Phenylketonuria with a Study of Effect upon it of Glutamic Acid," Arch. Dis. Child., 26:487, 1951.

☆ U S. GOVERNMENT PRINTING OFFICE 1964 O—736-752